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Localisation of atrial natriuretic peptide immunoreactivity in the ventricular myocardium and conduction system of the human fetal and adult heart

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SUMMARY Atrial natriuretic peptide immunoreactivity was found in ventricular and atrial tissues with specific antisera raised to the amino and carboxy terminal regions of the precursor molecule. In 13 developing human hearts (7–24 weeks' gestation) the immunoreactivity was concentrated in the atrial myocardium and ventricular conduction system but it was also detected in the early fetal ventricular myocardium. Immunoreactivity in five normal adults was largely confined to the atrial myocardium although it was also found in the ventricular conduction tissues of hearts removed from 10 patients who were undergoing cardiac transplantation. The ventricular conduction system is an extra-atrial site for the synthesis of atrial natriuretic peptide. In the failing heart this synthesis may be further supplemented by expression of the gene in the ventricular myocardium.

It is possible that ventricular production of the peptide contributes to the raised circulating concentrations of atrial natriuretic peptide immunoreactivity found in severe congestive heart disease, particularly in patients with dilated cardiomyopathy.

Cardiac expression of the gene for atrial natriuretic peptide was originally thought to occur specifically in the atrium because immunoreactivity was localised in atrial myocytes of several mammals including man[1 2] and stored as the precursor molecule in secretory vesicles.[3-5] It has since been established, however, that both atrial natriuretic peptide messenger ribonucleic acid and immunoreactivity are also present in ventricular tissues[6-8] and cultures of ventricular myocytes.[5 9 10] Furthermore, the ventricular expression of the gene changes during development; the concentration of atrial natriuretic peptide transcripts (copies of messenger ribonucleic acid) and immunoreactivity was greater in fetal tissues than in adult tissues.[7 11 12] The localisation of ventricular immunoreactivity in the human heart has still to be established, but the subendocardial distribution of immunostaining in rat[13-15] and pig ventricles[16] has led to the suggestion that the immunoreactivity may be associated with the ventricular conduction system.

In patients with severe congestive heart disease ventricular expression of the atrial natriuretic peptide gene is augmented[17] and circulating concentrations of immunoreactivity are increased.[18-20] But it is not known whether the ventricular production of peptide is widespread or localised[21] or whether it is a feature common to the diseased heart or is associated with specific conditions. With these questions in mind, we used immunocytochemical techniques to investigate the occurrence of atrial natriuretic peptide immunoreactivity in the human conduction system and ventricular myocardium and to examine whether the pattern of distribution changes during cardiac development and disease. We also compared the localisation of ventricular immunoreactivity with that of the general neuroendocrine marker protein gene product 9·5[22] after initial findings indicated

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possible similarities in their distribution patterns of the two substances in conduction tissues.

Patients and methods

Three different antisera (code no XA6, AT7, and AG9) were raised to specific regions of the precursor molecule of human atrial natriuretic peptide by immunising rabbits with pure synthetic human pro-atrial natriuretic peptide 1–16 (cardiodilatin 1–16, Peninsula Laboratories Europe; antiserum XA6), and atrial natriuretic peptide Tyr^{41} 1–40 amino terminal fragments (cardiodilatin Tyr^{41} 1–40; antiserum AT7), and the pro-atrial natriuretic peptide 99–126 carboxy terminal fragment (α-atrial natriuretic peptide 1–28; antiserum AG9). We injected the peptide fragments that were conjugated to bovine serum albumin with glutaraldehyde or unconjugated as previously described.[3 23] We also used additional antiserum (code no 1648) directed against human protein gene product 9·5 (Ultraclone, Cambridge) that has been previously characterised.[22]

Tissues were obtained from 13 human fetuses after spontaneous or legal abortion (7–24 weeks' gestation) and at necropsy from five adults without cardiac or pulmonary complications (3–15 hour delay after death (table)). Samples of atrial and ventricular septal and free walls were also obtained during transplantation surgery from 10 patients with heart and lung diseases (table). The tissues were dissected so that the ventricular conduction system could be examined by sectioning mainly in the frontal plane (at right angles to the atrioventricular septal junction[24]). The collection of the tissues used in this study conformed to the ethical standards of the institutions in which they were obtained.

Table *Clinical features of patients whose hearts were examined for atrial natriuretic peptide immunoreactivity*

Patient No	*Sex*	*Age (yr)*	*H or H/L*	*Diagnosis or cause of death*	*NYHA*
				Necropsy specimens	
1	M	31		Road traffic accident	
2	F	60		Hodgkin's disease	
3	F	75		Septicaemia	
4	F	24		Asphyxia (hanging)	
5	F	65		Glucagonoma	
				Cardiac transplantation recipients	
1	M	17	H/L	Failure of previous lung transplant in patient with cystic fibrosis	IV*
2	F	2	H/L	Tricuspid atresia	III
3	F	17 mnth	H	Dilated cardiomyopathy	IV
4	M	59	H	Ischaemic heart disease	III
5	M	59	H	Dilated cardiomyopathy†	III
6	M	28	H	Adriamycin cardiomyopathy	III
7	M	6	H/L	Eisenmenger's syndrome	IV
8	F	28	H/L	Idiopathic pulmonary haemosiderosis	IV*
9	M	29	H/L	Sarcoidosis	IV*
10	F	21	H/L	Cystic fibrosis	IV*

*Grade of lung disease.
†Predominantly affecting the right side.
H, heart transplant; H/L, heart and lung transplant; NYHA, New York Heart Association.

Tissues were fixed by immersion for 16–24 hours at 4°C in a modified Bouin's solution containing 85 ml of 2% (w/v) paraformaldehyde in 0·1 mol/l phosphate buffer (pH 7·2) and 15 ml of saturated picric acid per 100 ml of fixative. We rinsed the tissues in several changes of phosphate buffered saline (0·01 mol/l pH 7·2) containing 15% sucrose and 0·1% sodium azide and then processed them for cryostat sectioning and indirect immunofluorescence staining. Briefly, sections (15 μm thick) were cut on a Bright cryostat at −25°C, mounted on poly-L-lysine coated slides, and air dried for an hour at room temperature. They were then immersed in buffered saline solution containing 0·2% Triton X-100 for 30 minutes, rinsed, stained with pontamine sky blue (BDH chemicals, UK), and rinsed again. Sections were subsequently incubated in primary antisera (diluted 1:200–1:3200) for 16–24 hours at 4°C, rinsed in buffered saline, and then incubated with fluorescein isothiocyanate labelled sheep anti-rabbit IgG (diluted 1:100; Wellcome Diagnostics, UK). We mounted the preparations in glycerol mixed in equal parts with buffered saline and examined them with a microscope (Olympus AH-2) equipped for epi-illumination.

To facilitate the identification of conduction tissues we cut additional sections for haematoxylin and eosin staining and some immunofluorescence preparations were also stained after photography. Blocks containing ventricular conduction tissues were cut sequentially so that the conduction system could be followed from the atrioventricular node through to the distal bundle branches. In control experiments, we saw no immunostaining for atrial natriuretic peptide when the primary antisera were preabsorbed with their respective antigens (10^{-5}–10^{-6} mol/l) for 24 hours at 4°C. Immunostaining for protein gene product 9·5 was abolished by preabsorption of the antiserum with the natural human antigen (2×10^{-7} mol/l). There was no cross reactivity between the amino (XA6, AT7) or carboxy terminal (AG9) directed antisera and the carboxy (α-atrial natriuretic peptide) and the amino terminal (cardiodilatin) peptide sequences respectively. The antisera also showed no cross reactivity with known cardiovascular neuropeptides.

Results

The distribution of immunostaining for all three antisera raised to the amino and carboxy terminal sequences of human pro-atrial natriuretic peptide 1–126 was identical in both fetal and adult heart tissues. The immunoreaction was generally more intense with the antiserum (AT7) raised to the larger amino terminal cardiodilatin fragment (atrial natriuretic peptide Tyr^{41} 1–40) but a characteristic perinuclear concentration of immunoreactivity was seen with all three antisera. There was strong immunoreactivity in the fetal atrial myocardium and some immunostaining of the ventricular myocardium. Immunostaining of the ventricular walls was concentrated in the subendocardial myocardium and least extensive in the epicardial regions. In all the fetal hearts immunoreactivity occurred in the subendocardial left and right bundle branches (fig 1). Some cells in the penetrating and branching bundle were also immunoreactive. The intensity of the immunostaining in the ventricular myocardium was less than in other regions of the fetal heart and when increasing dilutions of the primary antisera were tested it disappeared at lower dilutions than in the conduction system and atrial myocardium. The ventricular myocardial immunoreaction was most prominent in the fetal heart at 7–12 weeks' gestation whereas by 18–24 weeks it seemed to be mainly localised in subendocardial conducting cells. In contrast with the ventricular conduction system, cells in the sinus and atrioventricular nodes showed no immunostaining (fig 2).

Unlike the fetal heart, there seemed to be little expression of the atrial natriuretic peptide gene in ventricular conduction tissues obtained at necropsy from patients without cardiac or pulmonary complications. These tissues showed either no reaction or weak immunostaining that was confined to conducting bundle branches. Though the delay between death and obtaining the tissues was short (3–15 hours), in at least some of these cases it is possible that the apparent lack of immunostaining reflects a postmortem loss of immunoreactivity. In contrast,

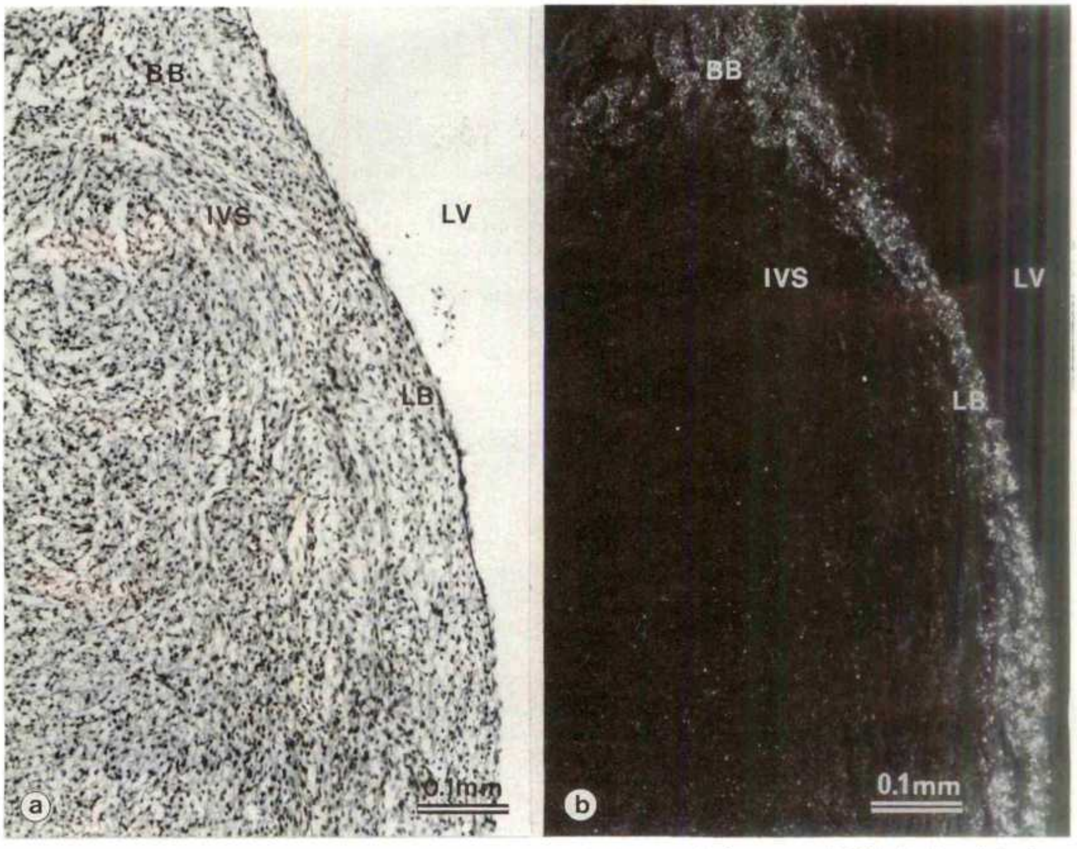

Fig 1 *Photomicrographs of adjacent longitudinal sections through the interventricular septum (IVS) of a 9 week fetal heart showing atrial natriuretic peptide immunoreactivity (b) in the branching bundle (BB) and left bundle (LB). Haematoxylin and eosin (a) and immunofluorescent staining (b). LV, left ventricle.*

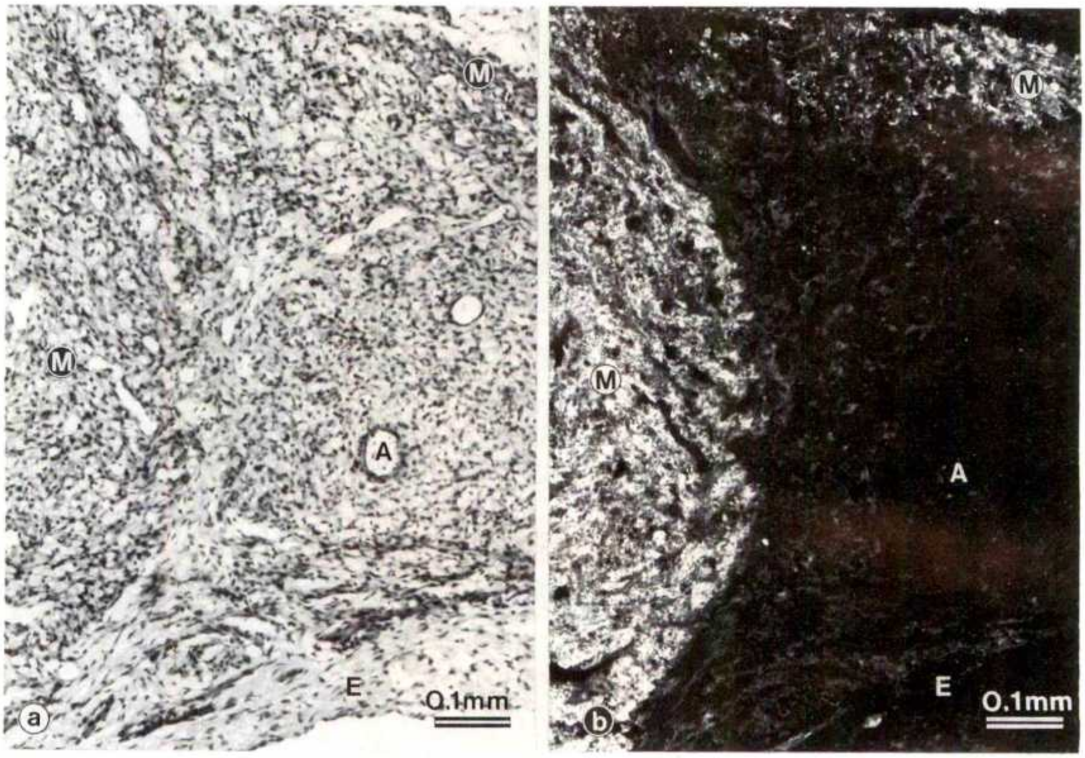

Fig 2 *Photomicrographs of the same section of human fetal sinoatrial node (18 weeks' gestation) and adjacent atrial myocardium (M) showing intense atrial natriuretic peptide immunoreactivity (b). The node is clearly distinct from the atrial myocardium and has a central artery (A). Section stained with haematoxylin and eosin (a) after the immunostained preparation (b) was photographed. E, epicardium.*

atrial natriuretic peptide immunoreactivity was regularly shown in ventricular tissues obtained at transplantation surgery. In these cases, the immunoreactivity was present in subendocardial elements of the conduction system. This localisation often coincided with that of protein gene product 9·5 (fig 3) which was usually localised in intrinsic neurones and cardiac nerves (rather than in conduction tissues) in the fetal heart and in tissues obtained at necropsy from patients without cardiac or pulmonary complications.

As well as finding that the atrial natriuretic peptide gene was expressed in ventricular conduction tissues, we also saw immunoreactivity in the ventricular myocardium of a patient (17 months of age) with dilated cardiomyopathy and end stage ventricular failure (table, case 3). Sheets of myocardial fibres with perinuclear rings of atrial natriuretic peptide immunoreactivity extended from the subendocardium deep into the myocardium of the interventricular septum, left and right ventricle walls, and papillary muscles (figs 4 and 5). We saw a gradient of immunostaining, similar to that seen in the fetal heart, across the ventricular wall, with positive fibres concentrated in the subendocardial regions. In the middle of the septum and in the free ventricular walls, scattered immunoreactive myocardial fibres were detected adjacent to interstitial regions containing small intramyocardial arteries. While the expression of the gene for atrial natriuretic peptide in the ventricular myocardium was prominent in this case of dilated cardiomyopathy it was not apparent in patients (2–59 years of age) with ischaemic heart disease, haemosiderosis, sarcoidosis, cystic fibrosis, and other forms of cardiomyopathy; in these patients immunoreactivity was only detected in ventricular conduction tissues.

Discussion

The results show that atrial natriuretic peptide immunoreactivity occurs in the ventricles of the human heart both during fetal development and in patients with diseases that eventually led to cardiac

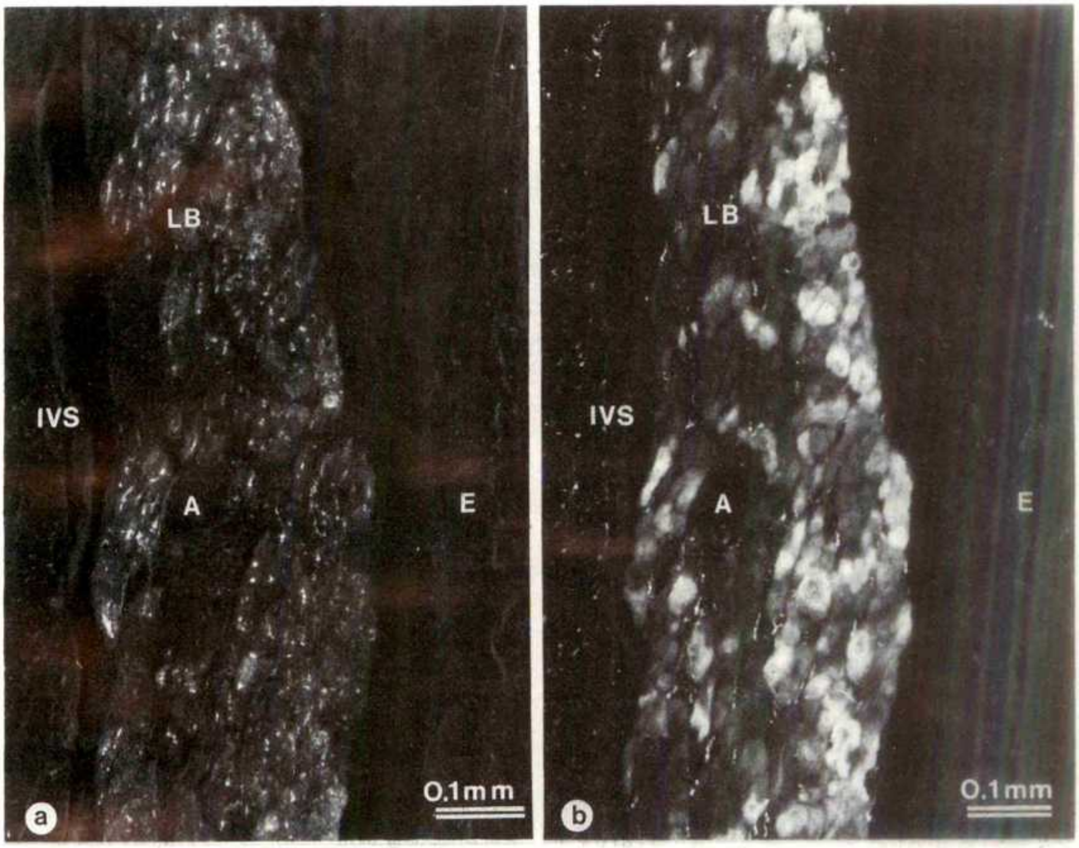

Fig 3 *Photomicrographs of adjacent sections of the interventricular septum (IVS) in an adult heart obtained at transplantation from a patient with cystic fibrosis (table, case no 10) showing the presence of both atrial natriuretic peptide (a) and protein gene product 9·5 immunoreactivity (b) in cells of the left bundle (LB) at the top of the interventricular septum. Protein gene product 9·5 immunoreactivity is also present in scattered nerve fibres in the bundle. E, endocardium of left ventricle; A, arteriole.*

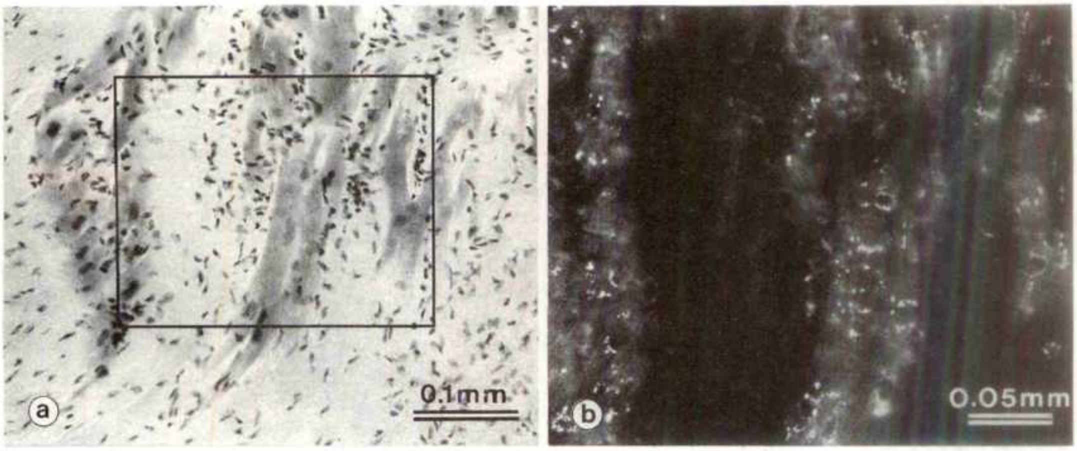

Fig 4 *Photomicrographs of the same section of left ventricular posterior wall from a transplant patient (table, case no 3) with dilated cardiomyopathy. The photomicrographs are shown at two magnifications and show subendocardial myocardial fibres with perinuclear rings of atrial natriuretic peptide immunoreactivity (b) dispersed in a dense fibrous tissue. Haematoxylin and eosin (a).*

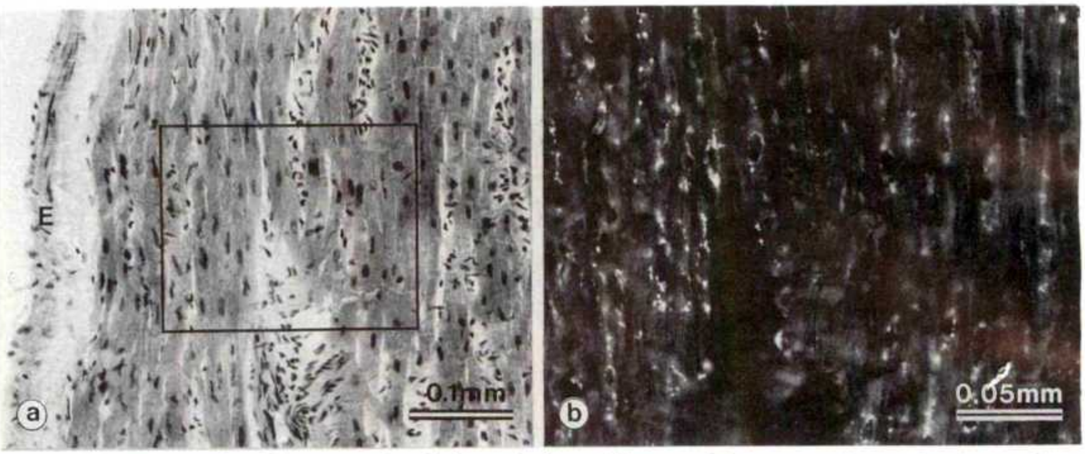

Fig 5 *Photomicrographs of the same section of left ventricular papillary muscle from a transplant patient (case no 3) shown at two magnifications and showing the presence of atrial natriuretic peptide immunoreactivity (b) in a continuous sheet of parallel myocardial fibres. Haematoxylin and eosin (a). E, endocardium of left ventricle.*

transplantation. It seems likely that the distribution of the immunoreactivity reported here reflects that of the precursor molecule (pro-atrial natriuretic peptide 1–126), rather than the smaller α-natriuretic peptide or cardiodilatin forms, since the antisera used specifically recognised carboxy and amino terminals of pro-atrial natriuretic peptide 1–126. Furthermore, the precursor molecule is the predominant molecular form found in extracts of both ventricular and atrial tissues.[5,10,12] The immunocytochemical findings indicate that there are developmental changes in the regulation of the expression of the atrial natriuretic peptide gene in human ventricular tissues. The decline in the extent of the ventricular immunostaining from early fetal to infant and adult life is similar to that reported for atrial natriuretic peptide immunoreactivity and messenger ribonucleic acid concentrations in tissue extracts of both rat[7,11] and human ventricles.[12] Though the mechanisms regulating gene expression in the ventricles are unknown it has been proposed that the decline in transcription during fetal development is related to the haemodynamic changes occurring during the transition from fetal to extra-uterine life together with the sensitivity of ventricular myocytes to the perinatal decline in glucocorticoid concentrations.[25]

Atrial natriuretic peptide immunoreactivity is confined to characteristic secretory vesicles,[1,2,4] but there is little information on the occurence of such vesicles in ventricular tissues. Vesicles were reported in human[26] and pig conduction tissues[16] and scattered vesicles were identified in hamster and rat ventricular myocytes[7,27] and these were immunoreactive.[5] The paucity of vesicles in ventricular cells has led to the proposal that there are two tissue specific secretory pathways for atrial natriuretic peptide in the heart. In the atria, natriuretic peptide is stored in numerous secretory vesicles whereas ventricular myocytes are thought to lack vesicles and secrete the peptide rapidly after synthesis.[7,10,27] None the less, both immunoreactivity and secretory vesicles were considerably increased in the ventricular myocardium of hamsters with cardiomyopathy and severe congestive heart failure.[27] The ventricular expression of the natriuretic peptide gene is also stimulated in the hypertrophied and volume overloaded rat heart[28,29] and in patients with severe congestive heart disease.[17] The immunocytochemical findings suggest that initially the expression of the gene in the diseased heart may be localised to conduction tissues, but in the case of dilated cardiomyopathy it seems that expression may become more widespread and include the ventricular myocardium. The distribution pattern of immunostaining for natriuretic peptide in the ventricular walls resembles that seen in both animal models of heart disease[29] and in human fetal hearts. These changes may indicate a persistence of or reversion to earlier fetal patterns of gene expression and are comparable with those observed for the cardiac myosin gene during development and in diseased human hearts.[30-32] On the other hand, the appearance of protein gene product 9·5 immunoreactivity in the ventricular conduction system is a novel finding that seems to have no fetal counterpart. It is of interest that a glycolytic isoenzyme, neurone specific enolase, that is found in high concentration in the nervous and neuroendocrine systems has also been detected in the adult human conduction system.[33] The functional significance of the occurrence of two distinct, so-called neuroendocrine marker proteins[34] in this tissue is not clear, but the localised distribution pattern of the immunostaining indicates a specific association with ventricular conduction cells containing natriuretic peptide, that is not seen in normal atrial and ventricular myocardium.

The localisation of immunoreactivity for atrial natriuretic peptide in the human ventricular conduction system extends earlier observations in the rat[13–15] and pig heart[16] and indicates that expression of the natriuretic peptide gene may be a general feature of the mammalian conduction system. A differential distribution of immunoreactivity was seen in the human fetal heart at mid-gestation and in the explanted adult heart at transplantation, with immunoreactivity being present in conduction cells rather than in the atrioventricular node or ventricular myocardium. This pattern of immunostaining is consistent with the view that conducting fibres have a separate origin from the atrioventricular node and ventricular myocytes.[35] Circulating concentrations of atrial natriuretic peptide immunoreactivity are highest in the coronary sinus. This has also been shown to be the main site of venous drainage from the interventricular septum and conduction tissues.[36,37] While it is possible that in the failing or hypertrophic heart the ventricular production and release of the peptide makes an important contribution to circulating concentrations, it seems doubtful whether the conduction system could have an endocrine role like that proposed for the atria. We do not know whether the atrial natriuretic peptide inflences impulse conduction in the heart, but its release does appear to be modulated by changes in atrial[18,19,38] and ventricular rhythm.[39] In addition to serving a hormonal function, the peptide could also act locally to influence the contractility of the ventricular myocardium.[40]

We found atrial natriuretic peptide immunoreactivity in the human ventricular conduction system and myocardium as well as in atrial tissues. This raises the question of whether the natriuretic peptide should be described as "atrial" or "cardiac". Production of the peptide within the ventricles depends on the stage of development. In the diseased heart there seems to be persistence of or reversion to patterns of atrial natriuretic peptide gene expression seen in earlier fetal life.

Antisera to human α-atrial natriuretic peptide and cardiodilatin sequences were produced in conjunction with Professor S R Bloom. We thank Mrs P Harley for technical assistance. This work was supported by the British Heart Foundation.

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Electrocardiographic prediction of coronary artery patency after thrombolytic treatment in acute myocardial infarction: use of the ST segment as a non-invasive marker

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SUMMARY The predictive value of the measurement of changes in ST segment elevation was assessed as a non-invasive marker of coronary artery reperfusion after thrombolytic treatment. Forty five patients with acute myocardial infarction (23 anterior, 22 inferior) of less than six hours' duration were given thrombolytic treatment by either the intravenous (n = 28) or the intracoronary route (n = 17). A proportional value for the shift in ST segment, termed the fractional change, was calculated both from 12 lead electrocardiograms and from the Holter tape for each patient. Coronary artery patency in an initial group of 22 patients (training group) was associated with a fractional change value of ⩾0·5 (100% specific, 88% sensitive by Holter analysis; 100% specific, 94% sensitive by 12 lead electrocardiogram). This rule performed well when it was applied to a test group of 17 patients (100% specific, 93% sensitive by Holter analysis; and 67% specific, 93% sensitive by 12 lead electrocardiogram). Linear discriminant analysis was then used to determine which features gave the best separation of those in whom there was reperfusion and those in whom there was not. This gave 100% specificity and 100% sensitivity when applied to the training group for either the 12 lead electrocardiogram or Holter monitoring. When it was applied to the test group, the sensitivity was maintained at 100%, but the specificity dropped to 33% irrespective of whether the basis of the test was Holter monitoring or the 12 lead electrocardiogram.

These results suggest that a fractional change of ⩾0·5 calculated from a single lead showing myocardial injury is a useful non-invasive marker of reperfusion. The technique can be applied to either 12 lead electrocardiograms or Holter monitoring. The use of a more complex classification increased the sensitivity of the test at the expense of its specificity.

Thrombolytic agents are increasingly used to treat patients with acute myocardial infarction. The immediate therapeutic objective is to obtain coronary artery reperfusion, which can only be confirmed definitely by coronary angiography. This invasive technique carries an inherent risk and is limited to major cardiac centres with facilities for cardiac catheterisation. Initially, administration of streptokinase required angiography for selective coronary artery infusions,[1] but subsequently intravenous infusions of streptokinase were shown to be effective.[2 3] More fibrin specific agents, such as anisoylated streptokinase plasminogen activator complex (APSAC)[4] and tissue plasminogen activator (tPA),[5] are also effective when given intravenously. The feasibility of giving thrombolytic agents intravenously to large numbers of patients was established by the recent GISSI study[6] and ISIS 2 study.[7] Emergency coronary angiography is not now needed for the administration of thrombolytic treatment, but there is a need for non-invasive physiological markers to identify coronary artery reperfusion.

The electrocardiogram is widely used in the clinical diagnosis of acute myocardial infarction and the

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time course of changes in the ST segment is well known. Analysis of the reduction in ST segment elevation, recorded by epicardial and precordial electrodes, was used to reflect coronary artery reperfusion in animal models,[8] and surface mapping techniques were applied during clinical thrombolysis.[9]

We have studied the ST segment changes occurring in patients during thrombolytic treatment with a view to devising a simple, sensitive, widely applicable technique to detect successful reperfusion non-invasively.

Patients and methods

We studied 45 patients (age range, 39–75, mean 58·5) with 23 anterior infarcts (in 18 men and five women) and 22 inferior infarcts (in 16 men and six women) who were admitted a mean (SD) of 2·7 (1·6) hours after the onset of pain. Patients were treated with thrombolysis if they had: (*a*) cardiac pain lasting at least 30 minutes but less than six hours by the time of admission to the coronary care unit; and (*b*) confirmatory electrocardiographic evidence of myocardial infarction (ST elevation ⩾1 mm in at least two standard limb leads or 2 mm ST elevation in at least two precordial leads). Patients were not treated with thrombolysis if they had (*a*) a history of bleeding diathesis, (*b*) a recent cerebrovascular accident, (*c*) peptic ulceration, or (*d*) severe renal or hepatic disease. Informed consent for administration of thrombolytic agents and for coronary arteriography was obtained in both groups.

The patients were admitted to the coronary care unit of Stobhill General Hospital and thrombolytic treatment was given according to the current coronary care protocol. Seventeen patients were given streptokinase by the intracoronary route, and 28 were given intravenous anisoylated plasminogen streptokinase activator complex (APSAC) (Eminase). The division of these patients into these groups depended on the current treatment and was not affected by the clinical severity of the illness on admission.

INTRACORONARY GROUP

Emergency coronary arteriography was performed (Judkins' technique) within the coronary care unit with an image intensification system (Siemens 2H-2N) and a high quality video tape recorder for permanent data storage.[10] The occluded infarct related artery was identified and streptokinase 250–500 000 units was infused selectively or subselectively over 30–45 minutes. The presence or absence of coronary artery reperfusion was determined visually at the end of the infusion.

INTRAVENOUS GROUP

Anisoylated plasminogen streptokinase complex (APSAC) (30 mg) was given over five minutes. Angiography was not performed before treatment, but coronary artery patency was confirmed by arteriography performed at 90 minutes after treatment. Angiography was delayed in some subjects until haemodynamic or electrical stability was achieved.

ELECTROCARDIOGRAPHIC ANALYSIS

Holter monitoring

On admission to the coronary care unit, 24 hour continuous electrocardiographic monitoring was started with an Oxford Medilog II system. Recording electrodes were placed in a modified V5 position. The tapes were analysed with a Reynolds Medical Pathfinder by an ST segment trend analysis. The ST segment elevation was measured as a pretreatment control value (M_1) and a second measurement (M_2) was made two hours after intracoronary treatment and three hours after intravenous thrombolytic treatment. The value after treatment was calculated as a proportion of the control value and this index was called the fractional change (fig 1). With complete reversal of the ST segment elevation the fractional change is one or a number near to one (fig 1a). If the ST segments remain elevated to the same degree the fractional change is around zero. When the ST segment elevation increases because of infarct extension, the fractional change is negative (fig 1b).

Twelve lead electrocardiograms

Conventional 12 lead electrocardiography was performed with a Hewlett-Packard Electrocardiograph 4700A on admission and at a mean (SD) of 302 (141) min after admission. The positions of electrodes on the chest were marked to ensure reproducibility. ST segment elevation was measured at the J point, and the lead showing the most ST segment elevation was taken for serial analysis. The fractional change was calculated in the same way as it was for Holter monitoring. In both studies, the electrocardiograms were read blindly without knowledge of the angiogram results.

STATISTICAL ANALYSIS

Linear discrimination was performed on an ICL2980 main frame computer (program *BMDP* (P7M)[11]). The patients were randomly subdivided by a random number generator into two groups: one a training group of 22 for devising a rule and a second test group of 17 for checking it. The sensitivity measures the ability of a test to detect genuine instances of reperfusion and was expressed as the number of cases of reperfusion detected by the non-invasive test as a percentage of angiographically confirmed reperfusions. Specificity measures the ability of a test to

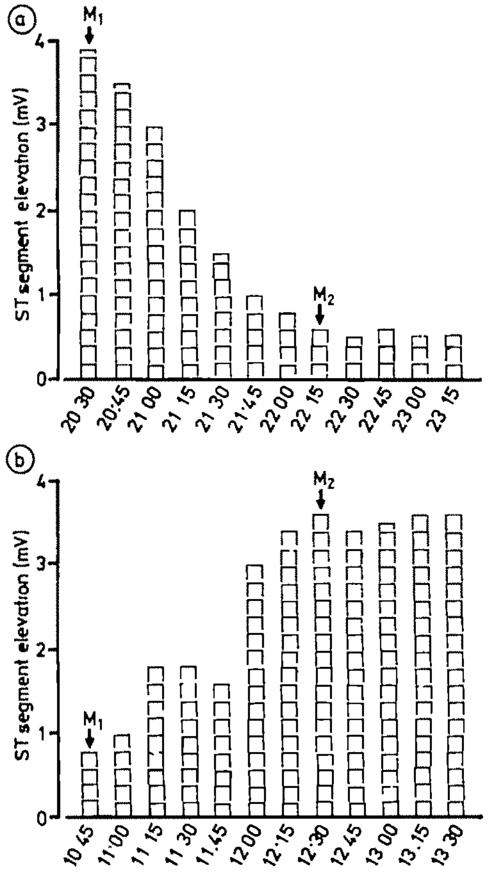

Fig 1 *Typical examples of ST segment analysis from Holter monitor recordings in patients treated with intracoronary thrombolysis. (a) A successful reperfusion. (b) No reperfusion. Measurement M_1 was made on admission before treatment and M_2 two hours after treatment. The fractional change was calculated as $(M_1 - M_2) - M_1$. For (a) the fractional change is 0·85 ((3·9 − 0·6) ÷ 3·9) and for (b) it is −3·5 ((0 8 − 3 6) − 0·8).*

detect genuine instances in which there has not been reperfusion. It was expressed as the number of true cases of non-reperfusions detected by the non-invasive test as a percentage of angiographically confirmed cases of non-reperfusion.

Results

We analysed the electrocardiographic recordings of 39 subjects (six were not analysed). In four patients there was incomplete collection of data because the Holter monitoring tapes were technically inadequate, in one patient a left bundle branch block precluded interpretation of the ST segment, and in another patient the coronary arteriogram was inadequately visualised. The remaining 39 patients were randomly split into a training group (n = 22) and a test group (n = 17). Figure 2 shows scatter of the values of fractional changes for these two groups, both for the Holter tapes and the 12 lead electrocardiograms. The arteriographic patency rate of the coronary arteries was high (79·5%). Because the ST segment elevation is not completely reversed after coronary artery reperfusion, several arbitrary values of ST segment reduction were examined including 0·25, 0·5, and 0·75. A fractional change of 0·5 seemed to be the most useful value for separating those cases with reperfusion from those without. Six of the total of nine patients without reperfusion showed more ST segment elevation on the second electrocardiogram, resulting in a negative fractional change. In the three in whom the elevation of the ST segment was reduced without angiographic evidence of reperfusion the fractional change was <0·5. There were no differences in mean (SD) ST segment elevation on the presentation electrocardiogram between those who had reperfusion (3·8 (2·4) mm) and those who did not (3·1 (2·1) mm). The table gives the specificity and sensitivity in both the training and test groups for detecting reperfusion by a fractional change of 0·5. We then used linear discrimination with a *BMDP* program to devise a rule that would give maximum discrimination between the two groups—reperfusion and non-reperfusion. This program used the following electrocardiographic variables: fractional change with Holter monitoring (FCH), fractional change with 12 lead electrocardiogram (FC), M_1 (height of ST segment on admission), and M_2 (height of ST segment after treatment). We derived the following classification functions for the training group:

(a) *Using fractional change with Holter monitoring*

Reperfusion = $-3{\cdot}31 + (2{\cdot}42 \times \text{FCH}) + (1{\cdot}45 \times M_1) - (1{\cdot}36 \times M_2)$

Non-reperfusion = $-8{\cdot}48 - (4{\cdot}74 \times \text{FCH}) - (1{\cdot}03 \times M_1) + (3{\cdot}72 \times M_2)$

(b) *Using fractional change*

Reperfusion = $-2{\cdot}80 + (1{\cdot}21 \times \text{FCH}) + (1{\cdot}28 \times M_1) - (0{\cdot}87 \times M_2)$

Table *The specificity of a fractional change of ≥0·5 for the detection of reperfusion*

ECG variable	*Specificity (%)*	*Sensitivity (%)*
Fractional change by Holter monitoring		
Training group	100	88
Test group	100	93
Fractional change by 12 lead ECG		
Training group	100	94
Test group	67	93

ECG, electrocardiogram.

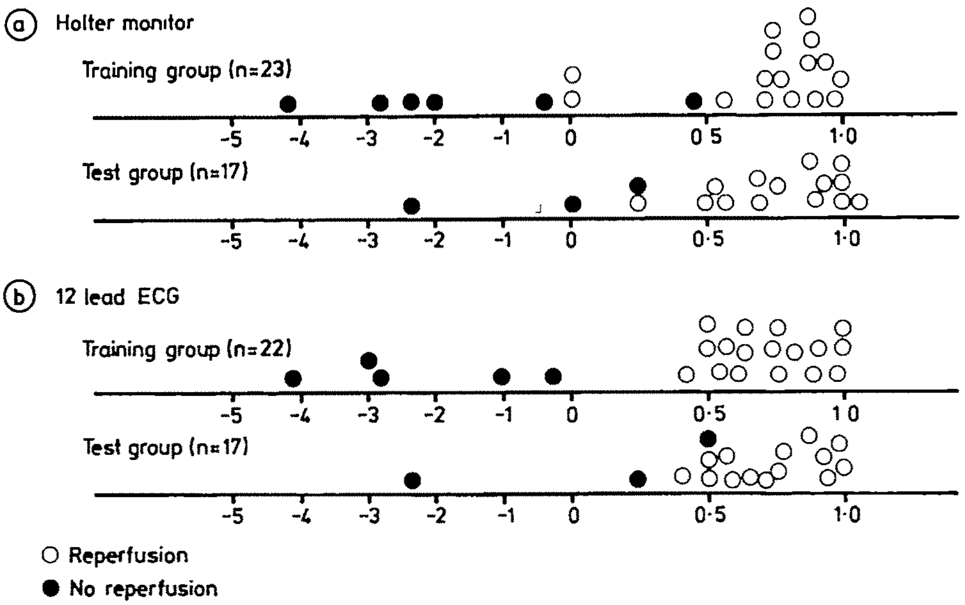

Fig 2 *Scatter diagrams showing fractional changes calculated for Holter monitoring (a) and 12 lead electrocardiograms (b).*

Non-reperfusion = $-7{\cdot}01 + (-3{\cdot}09 \times \text{FCH}) - (0{\cdot}57 \times M_1) + (2{\cdot}64 \times M_2)$

To use these classification functions, the value of the fractional change (either from 24 hour tapes or 12 lead electrocardiograms) and the height of the ST segment on admission and after treatment must be known. These values were substituted into the formulas for reperfusion and for non-reperfusion; the patient was identified as belonging to the group formula that gave the higher value. For example, a patient with an FCH of 0·65 and $M_1 = 3{\cdot}5$ and $M_2 = 1{\cdot}7$, gives values of 1·03 for the reperfusion group and −8·84 for the non-reperfusion group. As 1·03 is > −8·84, these findings are consistent with reperfusion.

This form of discriminant analysis correctly identified all the patients in the training group (sensitivity 100%, specificity 100%). The sensitivity was the same in the test group, but the specificity dropped to 33%. This dramatic fall in specificity is partly attributable to the small numbers in the test group with no reperfusion (n = 3) and the fact that only one of these three patients was correctly identified.

Discussion

These results confirm the usefulness of ST segment analysis as a non-invasive predictor of coronary artery patency after thrombolytic treatment in patients with acute myocardial infarction. This technique can therefore identify patients who may require further pharmacological treatment to prevent reocclusion, or who may require subsequent invasive investigation before coronary angioplasty or bypass surgery for residual arterial stenosis. A fractional change of ⩾0·5 was more specific but not as sensitive as the more complex classification functions derived from linear discrimination. The fractional change derived from the Holter monitor was more specific but not quite as sensitive as that calculated from the 12 lead electrocardiogram. The lack of sensitivity was the result of a fractional change of zero in two patients in whom angiography confirmed reperfusion. These two patients had inferior myocardial infarction, and it may be that the standard lead positions used are less effective in showing myocardial injury in the inferior wall of the heart. In addition, the differences in sensitivity and specificity between the Holter tape and the 12 lead electrocardiogram may to some extent reflect the differences in times over which the change was measured: two or three hours with the 24 hour tape and a mean of five hours with the 12 lead electrocardiogram. This was the earliest period that a 12 lead electrocardiogram was performed after the patient's return to the coronary care unit after angiography. Measurement of the fractional change over a longer period may have produced fractional changes that were nearer to 1, because the natural sequential decline in the elevation of the ST segment would have contributed to this greater value. In theory, extending the time over which the electrocardiograms were performed may have reduced both the sensitivity and specificity and have overestimated the reperfusion rate. This, however, does not seem to be a problem in our study, but it suggests that the earlier determination of the fractional change is more appropriate.

After the work of Pardee, who recognised that ST segment elevation was a marker of coronary occlusion,[12] many experimental and clinical studies have attempted to use this functional electrocardiographic marker as an index of ischaemic injury and to assess pharmacological interventions designed to limit infarct size.[13 14] Although previous studies have shown a rapid sequential change in ST segments after successful thrombolysis[3 9] the usefulness of these changes in identifying reperfusion non-invasively was not studied. A disadvantage of this technique is that the ST segment may be altered by factors other than coronary occlusion such as pericarditis[15] or metabolic abnormalities including hyperkalaemia.[16] The presence of interventricular conduction defects, including right or left bundle branch block, or the use of a ventricular pacemaker will also invalidate this technique.[17]

The complex precordial mapping systems with on line computer analysis used by von Essen *et al* to determine ST segment changes after thrombolysis[9] is technically difficult, expensive, and limited to a few specialised cardiac centres. Madias *et al* suggested that the 12 lead electrocardiograph was more useful than anterior precordial mapping in diagnosing and following serial changes in patients with inferior myocardial infarcts.[18] Leinbach *et al* further confirmed that both the rate and degree of ST segment fall could be followed accurately by single leads that reflected the zone of maximum electrocardiographic injury.[19] We too were successful when we used a suitable precordial lead to show ST elevation in either a Holter tape or the standard 12 lead electrocardiogram.

Continuous electrocardiographic monitoring has the advantage of incorporating a computerised assessment of the ST segment change although it is more complex and time consuming to analyse. The 12 lead electrocardiogram is widely available, inexpensive, and reproducible and can be used quickly at the bedside to reach decisions regarding further management including drug treatment.

The best method for clinical use depends on the specificity and sensitivity of the test. These may change depending on the purpose for which they are being used. Reocclusion has been reported in up to 30% of patients after successful coronary artery reperfusion. Pharmacological regimens have recently been developed to prevent reocclusion. A test that is highly sensitive in detecting reperfusion will be of value in deciding which patients require follow on treatment. Comparison of reperfusion rates after administration of different thrombolytic agents would require a high specificity. Though we tried to validate our rule in training and test groups, both groups were small and this gives wide errors in estimation of confidence intervals for sensitivity and specificity. The test may need to be assessed in much larger groups.

It may be that the high percentage of patients in the non-reperfusion group who showed an increase in ST segment elevation resulting in a negative fractional change reflects reocclusion rather than just non-reperfusion. By definition reocclusion occurs only in vessels that initially have been reperfused; this would result in a biphasic curve on the ST segment printout. When we examined our patients none of them showed such a curve, and, in addition, no patient had recurrence of chest pain to suggest reocclusion. Application of this technique may be useful if studied over a longer period.

In summary, fractional change can be measured from a single lead by Holter monitoring techniques or from 12 lead electrocardiograms, by examining the lead showing most evidence of myocardial injury. It is a useful non-invasive marker of reperfusion, and a value of $\geqslant 0{\cdot}5$ predicts a patent artery within the time scale of our study. These changes are independent of the agent used and reflect adequate coronary artery perfusion; they may therefore be used to assess the efficacy of other thrombolytic drugs such as tissue plasminogen activator. Use of a more complex classification function increased the sensitivity at the expense of a decline in specificity. The discrimination of the test may be improved by the addition of other variables such as creatine kinase release curves or the presence or absence of reperfusion arrhythmias.

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Short term reproducibility of exercise testing in patients with ST segment elevation and different responses to the dipyridamole test*

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SUMMARY The short term reproducibility of exercise testing in 25 patients who had exercise induced ST segment elevation without baseline regional asynergy or a previous myocardial infarction, who had different responses to the dipyridamole test, was assessed. The patients performed a dipyridamole echocardiography test and a second exercise stress test. All underwent coronary arteriography. Seventeen patients had transient regional asynergy after dipyridamole (group 1) and either ST segment elevation (14 patients) or depression (three patients); a second group of eight had no asynergy and no electrocardiographic changes (group 2). The repeated exercise stress test was positive in 16 of the 17 patients of group 1 (11 with ST elevation and five with ST depression) and in two patients of group 2 (both had ST depression and one had coronary artery disease). The dipyridamole echocardiography test was positive in 17 of the 19 patients with coronary artery disease and was negative in all six patients without coronary artery disease. The repeated exercise stress test was positive in 17 of the 19 patients with coronary artery disease and in one patient without.

The dipyridamole echocardiography test and a repeated exercise stress test, but not a single exercise stress test, identified coronary artery disease causing exercise induced ST segment elevation.

In patients with effort induced ST segment elevation (without previous myocardial infarction) the dipyridamole echocardiography test may provide information on the underlying coronary structure and possibly the mechanism responsible for this uncommon electrocardiographic pattern on effort.[1]

Dipyridamole is a selective coronary arteriolar vasodilator, and has no known vasoconstrictive effects.[2 3] A positive dipyridamole echocardiography test with ST segment elevation is usually associated with severe coronary disease and suggests that fixed coronary lesions are responsible for the effort induced ST segment elevation.[1] Conversely, when the dipyridamole echocardiography test is negative for both echocardiographic and electrocardiographic criteria, a functional mechanism (spasm) is most likely to be the cause of ST segment elevation during exercise.[1 4 5]

The short term reproducibility of the exercise stress test may be another method of evaluating the underlying structure of the coronary arteries and the pathogenetic mechanism of effort induced ST segment elevation. Serial exercise stress tests in patients with angina that is predominantly caused by fixed lesions consistently demonstrate a fixed threshold,[6] while predominantly vasospastic angina is characterised by considerable variability of the electrocardiographic findings during repeat exercise stress tests.[7-9]

The aim of this study was to evaluate the short term reproducibility of the exercise stress test in patients with effort induced ST segment elevation and different responses to the dipyridamole echocardiography test. We tested the hypothesis that

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exercise stress tests that were reproducible and had a fixed threshold indicated clinically important coronary stenosis, whereas considerable variability indicated spasm.

Patients and methods

SELECTION OF PATIENTS

Twenty five patients (23 men and two women, mean (SD) age 53 (8) years, range 39–67) with exercise induced ST segment elevation without previous myocardial infarction or baseline asynergy at echocardiography or left ventriculography were enrolled in the study. Patients performed a dipyridamole echocardiography test and a repeat exercise stress test; all underwent coronary arteriography and left ventriculography.

Fifteen patients had documented variant angina (characterised by ST segment elevation at rest or after ergometrine provocation). No patient was taking medications.

EXERCISE STRESS TEST

Patients performed two multistage bicycle ergometer tests, with an initial load of 25 W and subsequent increases of 25 W every two minutes. A 12 lead electrocardiogram and systolic and diastolic blood pressures were recorded before exercise and every minute during exercise. The end points of the test were moderately severe chest pain, a diagnostic ST segment shift, maximal age related heart rate, and limiting dyspnoea or fatigue in the absence of ischaemia.

The test was repeated in each patient at a different time the next day: once in the morning between 8 and 11 am and once in the afternoon, between 3 and 6 pm.

Electrocardiographic tracings were noted as showing myocardial ischaemia when the ST segment altered its position by $> 1{\cdot}00$ mm 0·08 seconds after the J point occurred.

DIPYRIDAMOLE ECHOCARDIOGRAPHY TEST

Cross sectional echocardiographic and 12 lead electrocardiographic monitoring were performed during a dipyridamole infusion (0·56 mg/kg over 4 minutes).[10] In patients with a negative result the test was repeated the next day with a higher dose (0·56 mg/kg over 4 minutes followed by 4 minutes of no dose and then 0·28 mg/kg (half of the previous dose) over 2 minutes); the cumulative dose was therefore 0·84 mg/kg over 10 minutes.[11] The test was considered positive if there was transient asynergy of contraction (hypokinesia, akinesia, or dyskinesia) that had not been present during the baseline examination.[10 11]

Aminophylline (240 mg) was available, if needed, to reverse the effects of dipyridamole. During the procedure, the blood pressure and the electrocardiogram were recorded each minute. The electrocardiographic criteria for ischaemia during this test were the same as those used during the exercise stress test. Cross sectional echocardiograms were continuously recorded during and up to 20 minutes after dipyridamole administration.

We used a commercially available wide angle phased array imaging system (Hewlett Packard 77020). In the baseline studies whenever it was possible we imaged all the standard echocardiographic views. During the test new areas of abnormal wall motion were identified on multiple views by rapidly moving the ultrasound transducer through various positions.

According to a generally accepted qualitative analysis, the wall motion was graded as: hyperkinetic, normal, hypokinetic, akinetic, and dyskinetic.[10] Two independent observers analysed the videotapes. When there was disagreement about the results a third observer reviewed the study and decided the issue. None of the observers had access to the results of the angiographic or exercise stress tests before they graded the videotape. The dipyridamole test was repeated a second time on a different day.

ANGIOGRAPHIC STUDY

Patients underwent biplane left ventriculography and selective right and left coronary arteriography by either the Judkins' or the Sones' technique. Multiple views of each coronary artery were obtained, including craniocaudal views. Two independent observers assessed degrees of stenosis in the major coronary arteries shown by the angiograms. A vessel was considered to show significant obstruction if its diameter was narrowed by $> 70\%$. The severity of stenosis was estimated in the projection where it appeared to be most severe.

All the observers were unaware of echocardiographic and electrocardiographic data.

STATISTICAL ANALYSIS

The statistical significance was evaluated by the χ^2 test. A p value $< 0{\cdot}05$ was considered to be statistically significant.

Results

The table shows the results of the dipyridamole echocardiography test, of both exercise stress tests, and of coronary arteriography.

DIPYRIDAMOLE ECHOCARDIOGRAPHY TEST

In the 50 analysed tests (two for each patient), the evaluation by two observers was consistent in 46 and

Table *Results of dipyridamole echocardiography test, both exercise stress tests, and coronary angiography*

		Dipyridamole test		*Exercise stress tests*			*Coronary angiography (% stenosis)*		
Patient	*Age/sex*	*ECG*	*Asynergy*	*ECG*	*W*	*RPP*	*LAD*	*LCX*	*RCA*
1	56 M	↑V2–6	Septal-lateral	↑V2–6 ↑V2–6	75 75	176 179	90	0	50
2	66 M	↑V4–6	Septal	↑V4–6 ↑V4	75 75	165 175	100	0	40
3	57 M	↑D3, aVF	Posterior	↑D3 NC	100 100	224 214	0	0	90
4	60 M	↑D1, aVL, V2–5	Lateral-apical	↑D1, aVL, V2–5 ↑D1, aVL, V2–5	50 50	197 186	90	0	0
5	63 M	↑V2–3	Septal	↑V2–3 ↑V2–3	100 100	288 274	90	0	0
6	54 M	↑D1, aVL, V4–6	Lateral	↑V4–6 ↓V4–6	100 125	235 242	100	100	0
7	59 M	↑D3, aVF	Posterior	↑D3, aVF ↑D3, aVF	75 75	204 193	90	40	100
8	67 M	↓V4–6, D2–3, aVF	Posterior-lateral	↑aVL ↓D2–3, aVF, V4–6	50 50	214 211	0	100	75
9	46 F	↓V4–6	Septal	↑V2 ↑V3–4	100 75	190 175	90	0	0
10	42 M	↑D1, aVL, V2–4	Lateral-apical	↑aVL, V2–6 ↑aVL, V2	75 50	280 216	75	0	100
11	58 M	↑V2	Septal	↑V2 ↑V2	50 25	165 153	100	0	0
12	52 F	↑D2–3, aVF	Posterior	↑D2–3, aVF ↓V4	25 50	170 180	25	90	0
13	50 M	↑V2, aVL	Septal-apical	↑V2 ↑V2	100 100	195 160	90	0	50
14	49 M	↑aVL	Septal	↑aVL ↑aVL	50 75	165 198	100	0	40
15	47 M	↓V6	Apical	↑aVL, V6 ↑aVL, V6	75 75	182 168	90	0	0
16	53 M	↑V4	Septal-lateral	↑V3–5 ↑V2–5	50 50	150 161	90	0	0
17	46 M	↑aVL	Septal-apical	↑aVL ↓V2–5	25 50	239 248	100	0	0
18	49 M	NC	No	↑V2–4 NC	50 100	104 208	0	0	0
19	43 M	NC	No	↑V2* NC	100 100	315 322	75	0	0
20	49 M	NC	No	↑D1, aVL ↓V4	25 75	103 224	0	90	75
21	46 M	NC	No	↑V2–3* NC	75 75	276 280	50	0	0
22	64 M	NC	No	↑D2–3, aVF NC	50 75	162 199	0	0	40
23	60 M	NC	No	↑aVL NC	75 100	210 228	0	0	0
24	51 M	NC	No	↑D1, aVL NC	100 100	163 179	0	25	0
25	39 M	NC	No	↑V2–6 ↓V2–4	50 100	82 270	50	0	0

*After the end of exercise.
LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; NC, no changes; RCA, right coronary artery; RPP, rate pressure product.
↓ST segment depression; ↑ ST segment elevation; lateral, anterolateral wall; posterior, inferoposterior wall; septal, ventricular septum.

different in four, when the opinion of a third observer was the deciding factor.

This test identified two groups: group 1 (17 patients) with dipyridamole induced asynergy and either ST segment elevation (14 patients, figure) or depression (three patients); and group 2 (eight patients) in which dipyridamole did not induce asynergy that was detectable by either echocardiographic or electrocardiographic criteria.

The echocardiographic and electrocardiographic findings were the same in both tests. Coronary arteriography showed clinically significant coronary artery disease in all 17 (100%) patients in group 1 and in two (25%) of the eight patients of group 2 ($p < 0{\cdot}01$). The dipyridamole echocardiography test identified coronary artery disease in 92% of the patients who were positive by angiography.

EXERCISE STRESS TEST

The repeated exercise stress test showed diagnostic ST segment changes in 16 of 17 patients in group 1 (11 had ST segment elevation and five had ST

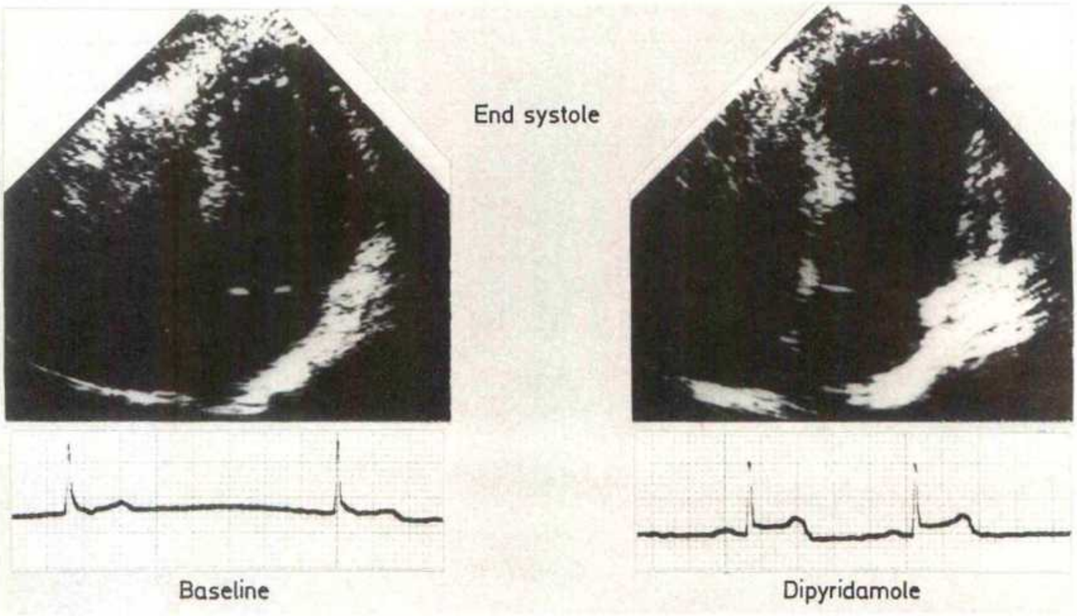

Figure *Cross sectional echocardiograms recorded at rest (left) and during dipyridamole induced ischaemia (right). There was a severe basal stenosis in the left anterior descending coronary artery. Echocardiographic images were taken from the apical approach, four chamber view. They show a normally contracting apex under baseline conditions that become akinetic during dipyridamole induced ST segment elevation (V4).*

segment depression) and in two out of eight patients in group 2 (both with ST depression) ($p < 0.01$). Exercise tolerance (expressed as the rate-pressure product) did not change substantially (> 20% of the mean of the two tests) in 16 of the 17 patients in group 1 and in four of the eight patients in group 2 ($p < 0.05$). The repeated exercise stress test was positive in 17/19 patients with coronary disease and in one patient without coronary disease. The repeated exercise stress test was 88% accurate in identifying coronary artery disease.

VARIANT ANGINA

We defined variant angina as angina at rest (assessed by two days of monitoring on either the coronary care unit or by Holter) or after ergometrine provocation that was associated with ST segment elevation. Ergometrine testing was performed in three patients; two of them had a positive test. Variant angina was present in eight of 17 patients in group 1 and in seven of the eight patients in group 2 (difference not statistically significant). None of the patients was in an active phase of the disease (> five attacks per day). In patients with angina at rest the average number of attacks per patient per day was 2·1 for group 1 and 2·5 for group 2.

Discussion

The coronary anatomy underlying effort induced ST segment elevation was identified by the dipyridamole echocardiography test and by the repeated exercise stress test but not by a single exercise stress test or a history of variant angina.

The induction of myocardial ischaemia by the dipyridamole test combined with simultaneous monitoring by 12 lead electrocardiography and cross sectional echocardiography gives useful information.[10 11] The echocardiographic criterion of ischaemia is much more specific and probably more sensitive than electrocardiography.[11] Furthermore, ultrasound imaging permits the site and extent of the ischaemic zone to be identified; these are not reliably shown by the electrocardiogram.[11] But dipyridamole induced ST segment elevation is a more specific marker of ischaemia than ST segment depression,[1] and in the highly selected population in this study we found that it was as good as echocardiography in identifying patients with clinically important coronary artery disease.

COMPARISON WITH PREVIOUS STUDIES

There is debate about the short term reproducibility of the exercise stress test in patients with effort induced ST segment elevation. De Servi *et al* and Brunelli *et al* showed a variable exercise threshold and multiple electrocardiographic patterns in patients with documented vasospastic angina undergoing repeat exercise stress testing.[8 9] Yasue *et al* in a study of 13 patients with variant angina, also found poor reproducibility for ST segment elevation on effort in 11 patients (five of them had < 70% coronary stenosis).[7]

In contrast, Specchia *et al* found reproducible ST segment elevation in four patients with variant angina. Coronary arteriography showed insignificant (< 70%) coronary lesions in three of them and a 75% stenosis in the other patients.[12] Waters *et al* also reported reproducible ST segment elevation in patients with variant angina and absent or mild (< 50%) coronary artery disease.[13] These "discrepancies" may not be real because the reproducibility of a test is mainly a function of the activity of the vasospastic disease (with vasospasm being more easily elicited on effort if patients are in a more active phase of the disease).[14] Variant angina is cyclical and clinical observations and laboratory findings depend on the phase in the disease process and on treatment.[13] All four patients studied by Specchia *et al*[12] had multiple spontaneous episodes of ST segment elevation at rest; five of the seven patients studied by Waters *et al*[14] had a spontaneous attack during the coronary angiography, without any provocative stimulus, indicating that they were in an active phase of the disease.

Though we agree that the cyclical nature of the disease must influence the results of screening it cannot explain the findings of our own study. Patients with dipyridamole induced ST segment elevation had more reproducible findings in the repeated exercise stress test, though they were in a less active phase of the disease than patients with negative dipyridamole echocardiography test—the average number of attacks per patient per day was lower in this group. These data draw attention to another fundamental factor that determines the short term reproducibility of the exercise stress test—the underlying organic coronary disease. Active coronary vasospasm is not the only pathogenetic mechanism of exercise induced ST segment elevation, and a severe stenosis can cause ST segment elevation on effort[15] or after dipyridamole[1] through a purely haemodynamic (non-vasospastic) effect.[16] In this event, because effort induced ST segment elevation is caused by organic factors it is not surprising that the electrocardiographic pattern is consistent in repeated exercise stress tests.

In patients in group 2, effort induced ST segment elevation was probably caused by vasospasm—the second exercise stress test was almost always the least abnormal. This is probably because of the inclusion/exclusion criteria of this study. All patients had ST segment elevation in the first exercise stress test and none had more than five anginal attacks per day. Under these conditions the second exercise stress test is more likely to give better results than the first one; also patients will be less anxious (a possible contributing factor to spasm) about a repeat test.

CLINICAL IMPLICATIONS

In the absence of previous myocardial infarction, elevation of the ST segment with exercise is considered to be specific for coronary spasm by some[4 5] and a reliable marker of very severe fixed coronary artery disease by others.[15 17 18] Both these views may need to be amended in the light of our findings. A negative repeated exercise stress test with a negative high dose dipyridamole echocardiography test strongly suggest that no haemodynamically significant stenosis is present,[11 19] even if superimposed functional factors may transiently impair the exercise capacity.[20] Conversely, a dipyridamole induced ST segment elevation must imply the presence of physiologically, as well as anatomically, severe coronary stenosis, which probably also limits exercise capacity.

Dr E Picano is the recipient of the Associazione Ricerca Medica research fellowship for ultrasonic diagnosis of atherosclerosis. Dr G A Klassen is from Dalhousie University, Halifax, Nova Scotia, Canada, and is presently spending a sabbatical year at the Instituto di Fisiologia Clinica del CNR.

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Value of a bipolar modified inferior lead in detection of inferior myocardial ischaemia

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SUMMARY Only bipolar leads are normally available for ambulatory monitoring. Bipolar precordial leads are reliable for detecting left coronary artery insufficiency, but may not detect changes caused by right coronary artery insufficiency. The magnitude and polarity of ST segment changes in a bipolar modified inferior lead and in CM5 were compared with those in standard electrocardiographic leads in 10 consecutive patients with acute myocardial infarction (eight inferior and two anteroseptal). The polarity of the ST segment in the modified orthogonal y lead was the same as that in aVF in all eight patients with inferior myocardial infarction and in six the size of the ST segment shift was identical in the two leads as well. In two patients the ST segment shift was larger in the modified orthogonal y lead than in aVF. In one of the two patients with anteroseptal myocardial infarction the polarity of the ST segment shift was the same in the modified orthogonal y lead and aVF. In the other patient it was slightly different. The CM5 lead did not reliably detect inferior myocardial ischaemia.

A modified orthogonal y lead is suitable for the detection of inferior myocardial ischaemia.

Several non-invasive techniques are available for the diagnosis of coronary artery disease. Ambulatory ST segment monitoring, however, is the only one that gives information on myocardial ischaemia during normal daily activity. The precordial leads and in particular CM5, which is the one most commonly used, reliably detect ischaemia in the anterior wall of the heart but may fail to detect right coronary artery insufficiency.[1] This may be because the recording sites are restricted to the anterior aspect of the thorax, and a lead representing the vertical axis of the body, such as y lead that is used in spatial electrocardiography, might be better for recording the activity of structures lying towards the back of the thorax including the inferior wall of the heart.

We have tested this hypothesis by comparing the recordings obtained from a modified orthogonal y lead with those of the standard electrocardiographic leads and CM5.

Patients and methods

We studied 10 consecutive patients with acute myocardial infarction. Nine patients had recent infarction, seven in the inferior wall and two in the anteroseptal wall. We studied one during premonitory ischaemia, which subsequently became inferior infarction. We identified the site of infarction from the characteristics of abnormal Q and T waves in the standard electrocardiogram, and the diagnosis was confirmed by increases in serum enzymes. We excluded patients with arrhythmia, conduction disturbances, or electrocardiographic indications of ventricular hypertrophy or strain or both. None of the patients was on digoxin or other antiarrhythmic drugs and none complained of chest pain during the recording period.

We recorded a standard 12 lead electrocardiogram before Holter monitoring (table). This electrocardiogram was used as a reference standard for the subsequent Holter recording.

In all patients we obtained a 30 minute Holter recording with a two channel Holter recorder (Spacelabs, model 90201). One channel recorded the modified orthogonal y lead. Both electrodes of this lead were placed just to the left of the spinal column.

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Table *Site of myocardial infarction and changes in the 12 lead standard electrocardiogram before Holter monitoring in the 10 patients*

		ECG changes in:		
Patient No	*Site of myocardial infarction*	*Inferior wall*	*Septum*	*Anterior wall*
1	Inferior, Q wave	Q wave, ST elevation	—*	—
2	Inferior, Q wave	Q wave, ST elevation	—	—
3	Inferior, Q wave	Q wave, ST elevation	ST depression	ST depression
4	Inferior, Q wave	Q wave, ST elevation	—	ST depression
5	Inferior, Q wave	Q wave, negative T wave	—	ST depression
6	Inferior, non-Q wave	Negative T wave	—	—
7	Inferior, Q wave	Q wave, ST elevation	—	ST elevation
8	Inferior lateral ischaemia	ST depression	—	ST depression
9	Septum, Q wave	ST depression	Q wave, ST elevation	—
10	Septum, non-Q wave	—	Negative T wave	—

*No change.

The negative electrode was positioned on the superior angle of the scapula and the positive one above the iliac crest. The other channel recorded lead CM5 with the electrodes in conventional positions.

The Holter recordings were produced as a two channel real time printout (25 mm/s) from a computer for Holter analysis (Spacelabs Arrhythmia-master 90101). The tapes were analysed by visual inspection. ST segment changes were measured 80 ms after the J point; we used a line drawn between two consecutive PR segments as the baseline.

Results

Figure 1 shows the ST segment level of the modified orthogonal y lead, aVF, and CM5. In patients who had inferior myocardial infarction shown by the standard electrocardiogram the ST segment of the modified orthogonal y lead resembled that of the aVF lead. Four patients with ST elevation in aVF (cases 1, 2, 3, and 7) showed similar changes in the recording from the modified orthogonal y lead. In two (cases 1 and 3) the degree of ST elevation in recording from the modified orthogonal y lead was identical with that in the aVF recording, and in two the elevation was higher than in aVF (+0·17 and +0·1 mV and +0·25 and +0·15 mV in cases 2 and 7 respectively). When there were no changes in the aVF recording there was none in the modified orthogonal y lead either (cases 4, 5, and 6). The aVF and y lead recordings also corresponded in patient 8 in whom recordings were obtained during an episode of posterolateral ischaemia that eventually progressed into an inferior infarction. In patient 8 the degree of ST segment depression was equal in aVF and the modified orthogonal y lead. In two patients with anteroseptal infarction (cases 9 and 10) the resemblance between aVF and the modified orthogonal y lead recording was less pronounced. Patient 9 showed ST segment depression of −0·13 and −0·20 mV in aVF and the modified orthogonal y recordings respectively. In patient 10 there was slight ST elevation in the modified orthogonal y lead but no changes in aVF.

In patients with inferior myocardial infarction the polarity of CM5 was the same as that in the aVF lead in only four patients (cases 1, 2, 5, and 7) (fig 1b).

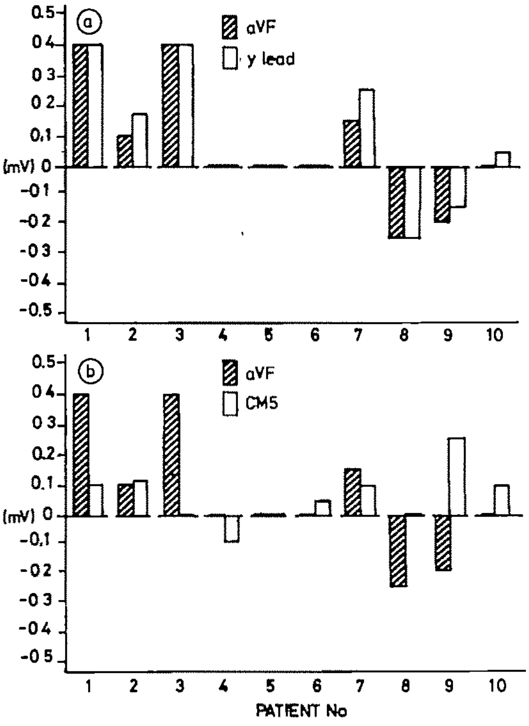

Fig 1 *(a) Polarity and magnitude of ST segment changes in aVF and modified orthogonal y leads in patients with acute myocardial ischaemia. (b) Polarity and magnitude of ST segment changes in aVF and CM5 leads in patients with acute myocardial ischaemia.*

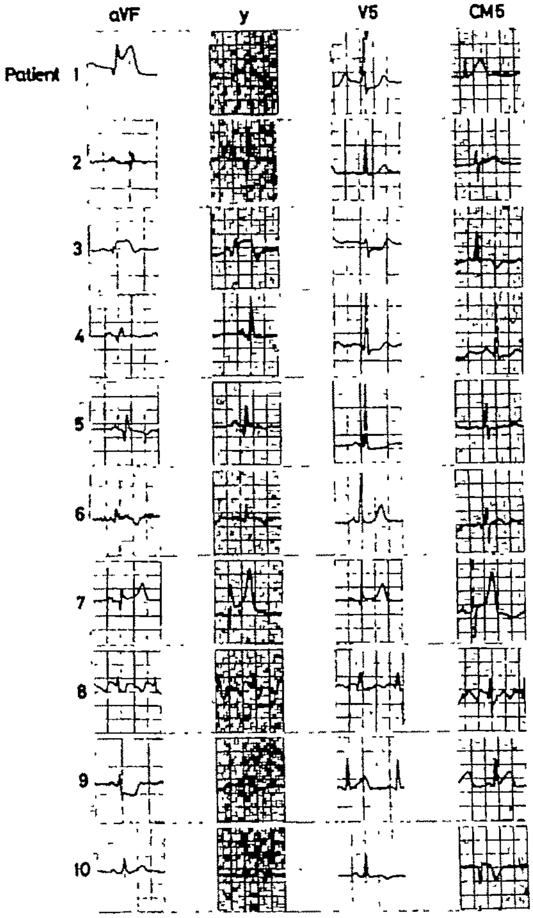

Fig 2 *Electrocardiographic changes in aVF, modified orthogonal y, V5, and CM5 leads in 10 patients with acute myocardial infarction.*

Discussion

Multiple lead electrocardiography is more sensitive than single lead systems for the detection of coronary insufficiency. In the standard electrocardiogram two bipolar (II, III) and one unipolar lead (aVF) are used to show inferior myocardial ischaemia. For Holter monitoring only two bipolar leads are usually available. CM5 is usually chosen as one of these because it is a sensitive detector of anterior myocardial ischaemia.[1 2] In patients with right coronary insufficiency, however, ST segment changes may be missed if only precordial leads are used.[1 2]

Cristal *et al* proposed a bipolar precordial "aVF-like" lead for the detection of electrocardiographic changes in the inferior wall.[3] They placed the negative pole under the outer third of the left clavicle and the positive pole at the left anterior axillary line in the 9–10th intercostal space. They found a good agreement in about two thirds of their patients between the modified lead and aVF. But precordial leads mainly record electrical forces generated by the anterior wall of the heart rather than those that originate in more distant cardiac structures such as the inferior wall. If an "aVF-like" electrocardiogram is recorded from a lead from the left precordium it does not prove that this lead is recording the same activity in the inferior wall as shown by the true standard aVF lead. An "aVF-like" electrocardiogram is more likely to resemble activity in the precordial leads recorded from the same region (V4–V6), which in the absence of ventricular hypertrophy or strain or both may resemble the aVF.[4] The opinion that leads recorded from the precordial area are unreliable in detecting ischaemia in the inferior wall was supported by the study of Quyyumi *et al.*[2] Using an "inferior-like" precordial lead, they found no changes in ST segment in patients with isolated right coronary insufficiency, unless similar changes were present in the CM5 lead.

We compared a modified inferior bipolar recording with a simultaneously recorded standard 12 lead electrocardiogram. By placing the electrodes away from the precordial area in a cranial-caudal position we obtained a bipolar lead resembling the unipolar aVF lead (fig 2). We found that in patients with ST elevation caused by a recent inferior infarction the changes in ST segment in this modified orthogonal y lead were the same as those seen in aVF. The findings in those two leads were also similar in those with ST depression caused by myocardial ischaemia or representing reciprocal changes during anterior infarction. Because the ST segment changes in CM5 did not sufficiently resemble the changes in aVF, CM5 should not be used to detect inferior ischaemia.

For Holter monitoring we recommend the use of a modified orthogonal y lead to record ischaemia in the inferior wall and a CM5 lead for the detection of ischaemia in the anterior wall.

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Effect of hyaluronidase on mortality and morbidity in patients with early peaking of plasma creatine kinase MB and non-transmural ischaemia

*Multicentre investigation for the limitation of infarct size (MILIS)**

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SUMMARY A multicentred, randomised, blind study was started in 1978 to compare propranolol or hyaluronidase with placebo in patients with acute myocardial infarction admitted within 18 hours of onset of symptoms. Patients were randomised to group A and received hyaluronidase, propanolol, or placebo, or, if propranolol was contraindicated, to group B and received hyaluronidase or placebo. Hyaluronidase (500 U/kg given every six hours for 48 hours) had no effect on mortality or infarct size in the overall population. Because spontaneous reperfusion was more common in patients with early peaking of plasma creatine kinase MB or non-transmural electrocardiographic changes or both, the results were reanalysed for two subgroups: those in whom plasma creatine kinase peaked < 15 hours after the onset of symptoms (early peak, $n = 184$) and those with a peak > 15 h after the onset of symptoms (late peak, $n = 546$). The distribution of time to peak activity of creatine kinase MB was similar in the hyaluronidase and placebo groups. In the early peak patients who were given hyaluronidase (groups A and B) total mortality and cardiac-specific four year mortality were significantly lower. This was most pronounced in group B in which the total mortality was 45% and cardiovascular mortality was 47% less than in the placebo group. Similarly, mortality from cardiovascular disease in patients (groups A and B) with non-transmural ischaemia (ST-T changes) given hyaluronidase was significantly lower, with group B showing a 50% reduction. In the subsets of patients with late peaking of creatine kinase MB or those presenting with transmural electrocardiographic changes there was no difference in total mortality or deaths from cardiac disease between those given hyaluronidase and those given placebo.

Hyaluronidase was associated with improved survival in patients with early peaking of plasma creatine kinase MB, suggesting the possibility of salvage of myocardium in patients who have early spontaneous reperfusion and possibly after therapeutic reperfusion.

The results of treatment with hyaluronidase in the Multicenter Investigation for the Limitation of Infarct Size (MILIS) were recently reported.[1] The trial included 431 patients randomised to placebo and 420 to hyaluronidase. Infarct size, the primary end point, and survival were not significantly different in those on placebo or hyaluronidase in the total population studied. None the less, a trend that favoured survival in the hyaluronidase group was noted in a prospectively defined subgroup of patients in whom propranolol was contraindicated (group B).

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Left ventricular ejection fraction, a secondary end point in patients randomised to group B, increased more between entry (pretreatment) and 8–10 days later in patients treated with hyaluronidase than in the placebo group; this difference was only of borderline significance ($p < 0{\cdot}06$).

To identify possible beneficial effects of hyaluronidase in subgroups of patients, additional analyses were performed retrospectively and these analyses form the basis of the present report. Although we recognise that such retrospective subgroup analyses must be interpreted with caution and cannot provide definitive results, they can provide useful insights and hypotheses for future testing.

Patients and methods

The overall design of the trial has been presented in detail[1-3]; only aspects pertinent to the subgroup analyses are presented here.

PROSPECTIVE SUBGROUPS

The patients enrolled in MILIS were suspected of having acute myocardial infarction on the basis of chest pain and electrocardiographic changes. Analysis of the plasma activity of creatine kinase MB confirmed myocardial infarction in 87% of randomised patients.[2] Patients were stratified prospectively into either group A (propranolol acceptable) or group B (propranolol contraindicated). The major reasons patients were entered into group B were moist rales involving a third or more of the lung fields (44%), ventricular rate of 55 beats/minute or less at randomisation or an episode of less than 40 beats/minute before anticholinergic treatment (30%), systolic arterial pressure of less than 100 mm Hg, a decrease of 50 mm Hg (23%), pulmonary oedema (19%), and asthma (15%). Group A patients were randomised to placebo, propranolol, or hyaluronidase, and group B patients to either placebo or hyaluronidase. Patients were only admitted to the trial within 18 hours from the onset of symptoms.

RETROSPECTIVELY IDENTIFIED SUBGROUPS

Since the start of the trial in August 1978, substantial information has accrued which indicates that Q wave myocardial infarction is frequently caused by thrombotic coronary occlusion.[4 5] There is also evidence to suggest that in some patients there is early spontaneous reperfusion[6 7] which is more likely to be associated with early peaking of plasma creatine kinase MB and with only ST-T wave changes rather than Q waves.[8 9] Presumably the early peaking reflects more rapid washout of the enzyme, which also occurs when pharmacological thrombolysis[10-12] and mechanical intervention produce reperfusion.[13 14] Non-Q-wave infarction is also associated with early peaking of plasma creatine kinase MB activity (a mean of 15 hours after onset of symptoms compared with patients with Q wave infarction in whom this peak occurs on average 17 hours after the onset of symptoms).[15] The results of early cardiac catheterisation show that Q wave infarction is associated with complete occlusion of the infarct related vessel. In contrast, non-Q-wave infarction is more likely to be caused by incomplete infarction,[16] suggesting that non-Q-wave infarction is associated with early reperfusion leaving extensive residual, viable but jeopardised myocardium.[17] The most recent implications for this hypothesis come from coronary angiography and thallium perfusion studies.[17] Extensive ischaemia (detected by thallium scintigraphy after exercise) and clinical events such as reinfarction and death were more common after non-Q-wave infarction than after Q wave infarction.

Retrospective analyses were performed to determine whether hyaluronidase had a different effect in patients suspected of undergoing spontaneous reperfusion because they had early peaking of plasma creatine kinase MB activity or non-Q-wave changes on the pretreatment electrocardiogram. We compared the effects of hyaluronidase and placebo on two end points: (*a*) mortality (both total and cardiovascular) and (*b*) the change in the left ventricular ejection fraction from the pretreatment value to that obtained 8–10 days after treatment. In the groups defined by the time to peak plasma creatine kinase MB we assessed only patients with confirmed myocardial infarction. In the group defined by the pretreatment electrocardiogram, patients were included if they satisfied the inclusion criteria, whether or not serial concentrations of plasma creatine kinase MB showed them to have sustained an acute myocardial infarction.

"Early peaking" of plasma creatine kinase MB activity was defined as occurring within 15 hours after onset of symptoms and "late peaking" as occurring more than 15 hours after onset. Fifteen hours represents the 25th percentile of the distribution of time from onset of symptoms to peak creatine kinase MB for MILIS patients with an abnormal increase in creatine kinase MB. We chose 15 hours because of the following observations in patients undergoing reperfusion. (*a*) Pharmacologically induced early thrombolysis leads to peaking of plasma creatine kinase MB around 12–16 hours after the onset of symptoms. (*b*) In patients with nontransmural infarction plasma creatine kinase MB peaks on average 15 hours after the onset of symptoms.[15] (*c*) Patients in whom spontaneous reperfusion is suspected reach peak plasma creatine kinase MB activity from 12 to 26 hours after the onset of symptoms,[16] which is similar to the time at which creatine kinase MB peaks after pharmacologically induced reperfusion.[11,12] Although there are limitations to the degree of correlation between the electrocardiogram and the anatomical extent of the infarct[18,19] in this study, "non-transmural ischaemic changes" are taken to refer to ST segment depression *without* new Q waves. "Transmural ischaemic changes" refer to ST segment elevation or abnormal new Q waves or both. Sixty nine patients in whom electrocardiographic classification into non-transmural or transmural ischaemia was not possible were excluded from analysis (for example, patients with conduction defects on the pretreatment electrocardiogram).

Patients were followed up three and six months after discharge. Subsequently, semi-annual reports on the health of the patient were completed either by personal or telephone interview. Long-term follow up was obtained from all but two of the 851 patients. Follow up efforts were extended six months after recruitment ceased to attain a minimum of six months of follow up on all randomised patients. Survival curves and mortality rates are based on a cut off of four years of follow up experience.

STATISTICAL ANALYSIS

We used t tests for quantitative data, χ^2 tests for qualitative data for baseline comparisons between treatments, actuarial life table techniques[20] and Cox proportional hazards methods[21] for the mortality analysis, and analyses of covariance for the comparisons of change in ejection fraction with different treatments. The generalised Savage (Mantel-Cox) statistic is reported in the unadjusted mortality analysis. The Cox proportional hazards analysis incorporated, as a covariate, a linear risk score[1] developed from baseline variables predictive of mortality in which there was some indication of imbalance between treatments. If the baseline ejection fraction used in the risk score was missing we used the mean ejection fraction among patients in whom the measurement was made. The covariance analysis of the change in the ejection fraction included the initial ejection fraction as an adjustment covariable.

Results

BASELINE CHARACTERISTICS

A total of 851 patients was analysed: 338 were in group A (172 randomised to placebo and 166 to hyaluronidase) and 513 were in group B (259 randomised to placebo and 254 to hyaluronidase). The baseline characteristics (27 variables) were compared among patients who received either placebo or hyaluronidase in the entire patient group (n = 851), in those in group B (n = 513), in those with early peaking of creatine kinase MB curves (n = 184), and in patients showing non-transmural ischaemia (n = 146). There were few significant differences between patients treated with placebo and hyaluronidase in the entire patient group or in any of the subgroups, indicating good balance between the placebo treated and hyaluronidase treated groups.

INFARCT SIZE INDEX

Data for the calculation of the infarct size index were adequate in 133 patients treated with placebo or hyaluronidase with early peaking of plasma creatine kinase MB activity and 491 with late peaking. Mean (SD) infarct size index in the group with early peaking was 12·6 (1·2) creatine kinase g eq/m^2, which was a mean of 67% of that in the late peaking group (18·9 (0·6), p < 0·0001). There was no significant difference in infarct size index assessed by plasma creatine kinase MB between the placebo treated and hyaluronidase treated groups for the total population or for prospectively identified subgroups.[1]

MORTALITY

A comparison of early and late peaking of plasma creatine kinase MB

There was no significant difference between the overall survival of the placebo treated and hyaluronidase treated patients over the four year follow up

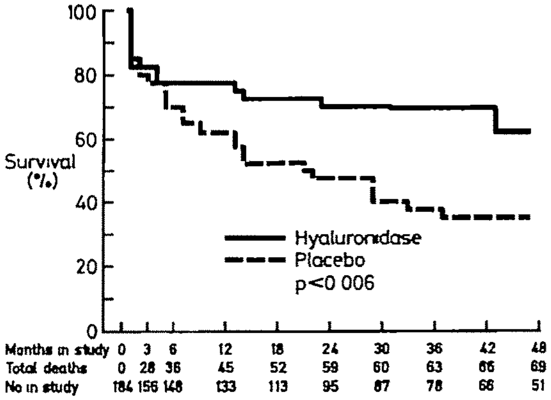

Fig 1 *Comparison of the survival curves over a four year period for patients treated with hyaluronidase or placebo who showed early peaking of plasma activity of creatine kinase MB (≤15 hours from onset of symptoms) in groups A and B combined. There was a statistically significant improvement in the survival of patients treated with hyaluronidase (p<0 006).*

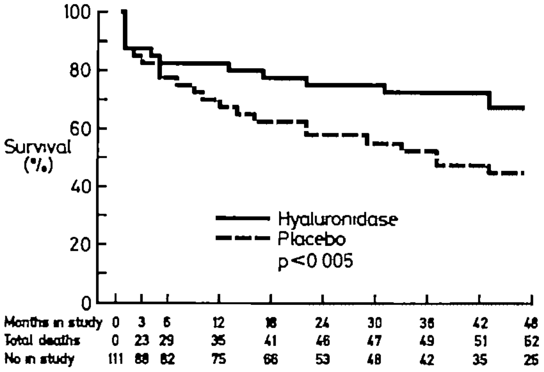

Fig 2 *Comparison of the survival curves over a four year period for patients treated with hyaluronidase or placebo who showed early peaking of plasma creatine kinase MB activity (≤15 hours from onset of symptoms) enrolled in group B. There was a statistically significant improvement in the survival of patients treated with hyaluronidase ($p < 0{\cdot}005$).*

interval.[1] None the less, a trend in favour of hyaluronidase was noted in group B (a mortality of 37% in placebo treated patients and 31% in hyaluronidase treated patients), but this difference did not achieve statistical significance. Similar results were obtained when the end point was restricted to deaths related to cardiovascular disease. Among all patients with early peaking of plasma creatine kinase MB (groups A and B), hyaluronidase treated patients had a four year mortality of 29% compared with 47% in the placebo group ($p < 0{\cdot}006$ unadjusted and 0·05 if adjusted for baseline differences (fig 1). The lower mortality in hyaluronidase treated patients with early peaking of plasma creatine kinase MB was most apparent in patients in group B in whom the four year mortality was 0·34, compared with the placebo group in which it was 0·62 (fig 2) ($p < 0{\cdot}08$ adjusted and 0·005 unadjusted). Similar results were obtained when the end point was death from cardiovascular disease (table 1). Unlike patients with early peaking of plasma creatine kinase MB, in those who had late peaking of plasma creatine kinase MB there was no difference in total mortality or cardiovascular mortality between patients treated with placebo or hyaluronidase in group A or group B, or in groups A and B combined.

In patients in group B who showed non-transmural electrocardiographic changes, both total mortality and deaths from cardiovascular disease were significantly lower in patients treated with hyaluronidase (table 3, fig 3). There were no differences in either the total or cardiovascular-related mortality between placebo and hyaluronidase treated patients in the group that showed transmural electrocardiographic changes on admission in either the overall group or in any of the subgroups.

In summary, comparison of the survival data between the placebo treated and hyaluronidase treated patients showed a beneficial effect in the hyaluronidase treated patients who showed early peaking of plasma creatine kinase MB and in patients who showed electrocardiographic findings that were characteristic of non-transmural ischaemia before treatment. This effect produced a lower frequency of both total deaths and those caused by cardiovascular disease in these subgroups of patients receiving hyaluronidase, and was present in the total patient population and in patients in group B.

EJECTION FRACTION

Prospective analyses

As indicated in the previous report,[1] for the total patient population the mean change in left ventricular ejection fraction measured by radionuclide

Table 1 *Comparison of cardiovascular mortality on different treatments by patient group and by time from onset to peak creatine kinase MB*

					p value	
Group	*Time to peak*	*Treatment*	*No*	*Crude death rate (%)*	*Unadjusted*	*Adjusted*
A and B	≤15 h	Placebo	87	43	0 01 (H)*	0 07 (H)
		Hyaluronidase	97	26		
	>15 h	Placebo	288	22	0 65	0 13
		Hyaluronidase	258	19		
A	≤15 h	Placebo	35	20	0 68	0 57
		Hyaluronidase	38	18		
	>15 h	Placebo	115	12	0 75	0 61
		Hyaluronidase	98	10		
B	≤15 h	Placebo	52	58	0 006 (H)	0 08 (H)
		Hyaluronidase	59	31		
	>15 h	Placebo	173	28	0 63	0 14
		Hyaluronidase	160	25		

*Indicates the treatment with the lower mortality H, hyaluronidase

Table 2 *Comparison of cardiovascular mortality on different treatments by patient group and pretreatment electrocardiographic findings*

Group	*Type*	*Treatment*	*No*	*Crude death rate (%)*	*p value* *Unadjusted*	*Adjusted*
A and B	Non-transmural	Placebo	74	38	0·04 (H)*	0·03 (H)
		Hyaluronidase	72	24		
	Transmural	Placebo	327	22	0·51	0·23
		Hyaluronidase	309	20		
A	Non-transmural	Placebo	26	15	0·51	0·46
		Hyaluronidase	30	23		
	Transmural	Placebo	140	14	0·61	0·37
		Hyaluronidase	122	11		
B	Non-transmural	Placebo	48	50	0·007 (H)	0·006 (H)
		Hyaluronidase	42	24		
	Transmural	Placebo	187	28	0·53	0·43
		Hyaluronidase	187	25		

*Indicates the treatment with the lower mortality: H, hyaluronidase.

ventriculography between pretreatment and 8–10 days after treatment was similar in the groups treated with placebo and hyaluronidase. In group B, however, the mean (SE) improvement in ejection fraction in patients treated with hyaluronidase (3·1 (1·0)) was significantly greater than in patients treated with placebo (0·5 (0·9), p = 0·06).

RETROSPECTIVE ANALYSES

Comparison of groups with early and late peaking of creatine kinase MB

There were no significant differences between patients treated with placebo and patients treated with hyaluronidase in the change in ejection fraction over the 8–10 days treatment for the group with late peaking of plasma creatine kinase MB. In patients in group B with early peaking of creatine kinase MB, however, there was greater improvement in patients receiving hyaluronidase (by 7·8 (2·1) units) than in the placebo group (3·2 (2·0) units) (p = 0·06) (table 3).

In patients with "non-transmural" electrocardiographic changes in group B, the ejection fraction rose more (9·7 (2·7) units) on hyaluronidase than on placebo (1·9 (2·1) units) (p < 0·007) (table 4). Treatment with hyaluronidase in patients with "transmural" electrocardiographic changes did not improve ejection fraction either in groups A or B or in groups A and B together. Thus patients with a significant improvement in ejection fraction were found only in group B and were characterised by electrocardiographic findings of non-transmural ischaemia. In patients in group B who had early peaking of plasma creatine kinase MB activity there was also a tendency for hyaluronidase to improve ejection fraction.

Patients with "non-transmural" electrocardiographic changes were evenly distributed between

Table 3 *Comparison of the change in ejection fraction on different treatments by patient group and time from onset to peak creatine kinase MB plasma concentration*

				Ejection fraction			
Group	*Time to peak*	*Treatment*	*No*	*Pretreatment*	*10 days*	*Change*	*p value*
A and B	≤15 h	Placebo	54	41·4 (1·9)	45·9 (2·6)	4·5 (1·6)	0·51
		Hyaluronidase	66	45·4 (2·0)	50·8 (2·0)	5·3 (1·6)	
	>15 h	Placebo	201	47·7 (1·1)	47·5 (1·0)	−0·1 (0·7)	0·26
		Hyaluronidase	188	47·0 (1·1)	48·1 (1·0)	1·2 (0·8)	
A	≤15 h	Placebo	23	44·3 (3·1)	50·5 (4·4)	6·3 (2·6)	0·25
		Hyaluronidase	27	48·6 (3·4)	50·4 (3·6)	1·8 (2·4)	
	>15 h	Placebo	88	49·3 (1·5)	49·9 (1·5)	0·5 (1·2)	0·65
		Hyaluronidase	75	51·3 (1·7)	52·0 (1·7)	0·7 (1·1)	
B	≤15 h	Placebo	31	39·3 (2·4)	42·5 (3·0)	3·2 (2·0)	0·06 (H)*
		Hyaluronidase	39	43·2 (2·4)	51·0 (2·4)	7·8 (2·1)	
	>15 h	Placebo	113	46·4 (1·5)	45·7 (1·4)	−0·7 (1·0)	0·27
		Hyaluronidase	113	44·1 (1·4)	45·6 (1·3)	1·5 (1·1)	

*Indicates the treatment associated with the greatest improvement in ventricular function: H, hyaluronidase.
Values shown are mean (SEM).

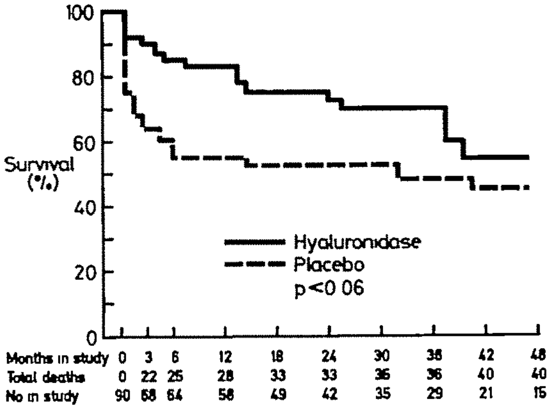

Fig 3 *Comparison of the survival curves over a four year period for patients treated with hyaluronidase or placebo who showed non-transmural changes on the pretreatment electrocardiogram and were enrolled in group B. There was an improvement in the survival of patients treated with hyaluronidase (p<0·06).*

placebo and hyaluronidase groups. None the less, there was a significant association between the type of electrocardiographic change and the time to peak plasma creatine kinase MB. Among the patients with transmural electrocardiographic changes, 23% had early peaking of plasma creatine kinase MB, whereas 38% of those with non-transmural changes had early peaking ($p < 0·0009$).

Discussion

Prospective analyses showed that hyaluronidase had a beneficial effect of borderline statistical significance on ejection fraction when it was given for 10 days to patients randomised to group B (about a third of all patients in MILIS). Retrospective analyses of patients with early peaking of plasma activity creatine kinase MB (25% of the total population) showed improved survival in those treated with hyaluronidase compared with those treated with placebo, with a reduction in both total mortality and deaths from cardiovascular disease. This effect, as in the prospective analyses, was most apparent in patients enrolled into group B. Improved ventricular function, reflected in a rise in ejection fraction from pretreatment values to 8–10 days on hyaluronidase, was also noted in group B patients with early peaking of plasma creatine kinase MB. Patients in group B who were treated with hyaluronidase who had evidence of "non-transmural" ischaemia on the qualifying electrocardiogram showed significant improvement both in survival and ejection fraction compared with placebo treated patients.

There were few significant differences between the baseline characteristics of the placebo and hyaluronidase groups with early peaking of plasma creatine kinase MB or non-transmural electrocardiographic changes; so baseline differences do not account for the beneficial effect of hyaluronidase, either in the group as a whole or those in group B. The similar results of the prospective and retrospective analyses and the combination of improved survival and function, together with the consistent observation that benefit was most noticeable in patients enrolled into group B probably imply some common mechanism.

The frequency of early peaking of plasma creatine kinase MB among the whole population was similar in patients who received placebo or hyaluronidase, indicating that hyaluronidase did not induce early peaking of plasma creatine kinase MB. Also in patients showing early peaking of plasma creatine

Table 4 *Comparison of the change in ejection fraction on different treatments by patient group and pretreatment electrocardiographic findings*

				Ejection fraction			
Group	*Type*	*Treatment*	*No*	*Pretreatment*	*10 days*	*Change*	*p value*
A and B	Non-transmural	Placebo	38	44·7 (2·5)	48·9 (2·7)	4·3 (1·8)	0·42
		Hyaluronidase	43	45·7 (2·8)	51·7 (2·4)	6·0 (2·1)	
	Transmural	Placebo	225	47·2 (1·0)	47·8 (1·0)	−0·6 (0·7)	0·27
		Hyaluronidase	212	47·0 (1·0)	48·8 (1·0)	1·8 (0·8)	
A	Non-transmural	Placebo	14	52·1 (4·1)	60·6 (4·0)	8·4 (3·2)	0·05 (P)*
		Hyaluronidase	16	52·4 (5·5)	52·3 (5·3)	−0·1 (2·9)	
	Transmural	Placebo	104	47·6 (1·4)	48·9 (1·5)	1·3 (1·1)	0·59
		Hyaluronidase	91	49·7 (1·5)	51·3 (1·6)	1·6 (1·1)	
B	Non-transmural	Placebo	24	40·3 (2·7)	42·2 (2·8)	1·9 (2·1)	0·007 (H)*
		Hyaluronidase	27	41·7 (2·8)	51·4 (2·4)	9·7 (2·7)	
	Transmural	Placebo	121	46·9 (1·5)	46·9 (1·4)	0·0 (1·0)	0·31
		Hyaluronidase	121	45·0 (1·4)	46·9 (1·3)	1·9 (1·1)	

*Indicates the treatment with most improvement in ventricular function H, hyaluronidase; P, placebo
Values shown are mean (SEM).

kinase MB, hyaluronidase did not affect infarct size, and therefore the beneficial effect of hyaluronidase was not the result of a reduction of infarct size. This is not unexpected, because treatment was started a mean of eight hours after the onset of symptoms. Instead, these findings suggest that the beneficial effect of hyaluronidase was mediated through some repair or healing process in the early recovery phase.

The early peaking of plasma creatine kinase MB with more rapid washout of creatine kinase reflects better perfusion of the area of infarction. In addition, the infarct size index in patients with early peaking of creatine kinase MB was only about two thirds of that in patients with late peaking of creatine kinase MB. This could result from spontaneous reperfusion, better collateral flow to the ischaemic myocardium in the distribution of the occluded artery, or incomplete obstruction at the initiation of infarction. In any event, it is postulated that early peaking of plasma creatine kinase MB and electrocardiographic changes of non-transmural ischaemia reflect interruption of the evolution of infarction by reperfusion.[15] The following evidence supports this postulate. (*a*) Infarcts were smaller in patients with early peaking of plasma creatine kinase MB; values in this study were 12·6 for early peaking and 18·9 creatine kinase gram equivalents per square metre for late peaking, despite increased washout of creatine kinase that could lead to overestimation of infarct size. Similarly, infarct size in patients with transmural changes averaged 17·5 creatine kinase gram equivalents per square metre compared with only 6·1 in patients with non-transmural infarction. (*b*) There is a tendency for myocardial damage to be restricted to the subendocardium in such patients.[22] (*c*) The electrocardiogram of patients with early peaking of plasma creatine kinase MB is more likely to show non-Q-wave infarction.[23 24] (*d*) The mortality and morbidity with a single event associated with early peaking of plasma creatine kinase MB are usually less than that associated with late peaking of plasma creatine kinase MB.[25 26] (*e*) Patients with non-transmural electrocardiographic changes have a greater tendency to be in an unstable condition and to have recurrent infarction,[23] presumably because of reocclusion of a spontaneously reperfused artery. (*f*) Coronary arteriography after infarction shows that most patients with non-transmural electrocardiographic changes have incomplete coronary occlusion, while the reverse is true of patients with "transmural" changes.[27 28] (*g*) Necropsy data show that contracture necrosis and haemorrhage are more common in non-Q-wave infarction than Q wave infarction,[29] suggesting that reperfusion is more common in the former group.

It is possible that the beneficial effects of hyaluronidase in patients with early peaking of creatine kinase MB and non-transmural electrocardiographic changes are related to the concomitant improved perfusion of the ischaemic and necrotic myocardium, which would provide a greater access for hyaluronidase to the injured myocardium and permit it to exert its beneficial effect. One hypothesis is that hyaluronidase accelerates recovery of function in surviving but "stunned"[30] myocardium, which would account for the improved ventricular function. Experimental studies have shown that hyaluronidase reduces swelling of ischaemic myocytes and increases perfusion of ischaemic myocardium,[31-34] an effect that might attenuate the "no reflow" phenomenon.[35 36] The hypothesis that the drug exerts its effect only with improved perfusion is consistent with the observation that we saw no beneficial effect in patients with late peaking of plasma activity of creatine kinase MB who presumably do not undergo spontaneous reperfusion.

Hyaluronidase has been shown to cause a short term increase in collateral blood flow[31] and a degradation product of hyaluronidase has been shown to stimulate the growth of new blood vessels.[36 37] It is possible that these effects, individually or in combination, could improve ventricular function and survival. Several studies have shown that patients with non-Q-wave infarction are likely to have early peaking of plasma creatine kinase MB and less extensive myocardial damage,[25 26] but because of subsequent recurrent myocardial infarction they experience a mortality after one year similar to that of patients with Q wave infarction.[26] It is possible that hyaluronidase, by stimulating growth of new vessels and collateral flow, could protect against such episodes or attenuate the extent of subsequent injury and thereby improve survival. The explanation for the selective effect of hyaluronidase on patients with early peaking of creatine kinase MB and non-transmural electrocardiographic changes or both may be that delivery of the drug to the jeopardised myocardium is enhanced in these patients.

The second major feature in patients who benefited from hyaluronidase is the consistency with which ventricular function and survival were improved in patients enrolled into group B. Group B patients were identified prospectively in MILIS on the basis of contraindications to propranolol, which included clinical evidence of heart failure, hypotension, and bradycardia. Group A in MILIS was a relatively low risk group; only 19% had suffered a previous myocardial infarction. The left ventricular ejection fraction at the time of admission was well maintained (mean 49%), and in placebo treated patients in group A the ejection fraction remained at an average of 50% 8–10 days after admission. The in-hospital mortality rate for placebo treated patients in group A was 4%, and the total one year and four year mortality rates were 12% and 15%, respectively. Even if hyalurodinase had a moderately beneficial effect, it could be detected only with a much larger sample of such patients. On the other hand, in group B the left ventricular ejection fraction was significantly lower at entry (mean 44%). In the placebo treated patients in group B, the ejection fraction at hospital discharge was 46%, and the in-hospital, one year, and four year mortality rates (12%, 25%, and 37%, respectively) were significantly higher than in group A. Thus in group B the extent of depression of left ventricular function and the mortality rate in the placebo treated group were such that even if only moderate improvement was produced by the drug it would be detected.

In conclusion, these retrospective findings provide supportive evidence for the beneficial effect of hyaluronidase that was suspected from the analyses carried out on prospectively identified subgroups. The beneficial effect was manifest by both improved ventricular function and survival and occurred in patients in group B. The principal features of the patient population that benefited from hyaluronidase were early peaking of plasma creatine kinase MB and non-transmural changes on the entry electrocardiogram. It may be that in the presence of acute infarction and reperfusion or residual blood flow, hyaluronidase exerts a beneficial effect, resulting in improved left ventricular function. In view of the widespread current use of thrombolytic treatment in patients with acute myocardial infarction, these findings may have important implications for the potential benefits when hyaluronidase is used in combination with reperfusion.

Because the data in this paper are derived from a retrospective subgroup analysis the strength of the conclusions is limited. Therefore, the hypothesis that hyaluronidase has a beneficial effect in these subgroups requires confirmation in prospective studies. In view of the internal consistency of the findings in this study, however, and the increasing importance of reperfusion treatment in acute myocardial infarction, which creates a patient group that is perhaps not unlike the retrospectively identified subgroup which benefited from hyaluronidase in MILIS, such studies deserve serious consideration.

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Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation

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SUMMARY Twenty two patients (four men, 18 women, mean age 56 years, range 21 to 88 years) with a history of rheumatic mitral stenosis were studied by cross sectional echocardiography before and after balloon dilatation of the mitral valve. The appearance of the mitral valve on the pre-dilatation echocardiogram was scored for leaflet mobility, leaflet thickening, subvalvar thickening, and calcification. Mitral valve area, left atrial volume, transmitral pressure difference, pulmonary artery pressure, cardiac output, cardiac rhythm, New York Heart Association functional class, age, and sex were also studied. Because there was some increase in valve area in almost all patients the results were classified as optimal or suboptimal (final valve area $< 1 \cdot 0$ cm^2, final left atrial pressure > 10 mm Hg, or final valve area $< 25\%$ greater than the initial area). The best multiple logistic regression fit was found with the total echocardiographic score alone. A high score (advanced leaflet deformity) was associated with a suboptimal outcome while a low score (a mobile valve with limited thickening) was associated with an optimal outcome. No other haemodynamic or clinical variables emerged as predictors of outcome in this analysis. Examination of pre-dilatation and post-dilatation echocardiograms showed that balloon dilatation reliably resulted in cleavage of the commissural plane and thus an increase in valve area.

Percutaneous balloon dilatation of the mitral valve is a promising new approach to the management of rheumatic mitral stenosis.[1–9] But at this early stage little is known about the criteria for patient selection or the mechanism by which balloon dilatation increases mitral valve area. Previous experience with closed surgical commissurotomy suggests that mitral valve pliability and the degree of leaflet thickening have an important effect on subsequent outcome.[10–15] Because cross sectional echocardiography shows the structure of the mitral apparatus, the severity of the stenotic lesion, and changes in chamber size[16 17] it should provide information that will predict the likely outcome of balloon dilatation.

Patients and methods

We studied the first 22 patients (four men and 18 women) who had percutaneous balloon dilatation of the mitral valve at the Massachusetts General Hospital. They were aged from 21 to 88 years (mean 56·6). All patients had a diagnosis of rheumatic mitral stenosis on the basis of history and clinical examination.

To identify features that might predict the result of balloon dilatation we analysed 18 variables assessed at the clinical, echocardiographic, and haemodynamic examinations performed before the procedure. The clinical variables included cardiac rhythm, New York Heart Association functional class, age, and sex. From the echocardiogram we assessed structural features of the mitral valve and subvalvar apparatus, including the initial mitral valve area (by planimetry), initial left atrial size, and the pre-valvotomy grade of mitral regurgitation (by Doppler echocardiography). The haemodynamic features measured at catheterisation before balloon dilatation included mitral valve area, transmitral pressure difference, cardiac output, pulmonary vascular resistance, and left ventricular end diastolic pressure. The degree of mitral calcification was also assessed by radiology.

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Table 1 *Individual clinical, haemodynamic, and echocardiographic results for the study group*

Patient	*Age*	*Sex*	*Rhythm*	*NYHA class*	*MVA-pre Gorlin*	*MVA-post Gorlin*	*Grad pre*	*Grad post*	*Pre LA-P*	*Post LA-P*	*PA pre*	*PA post*	*Outcome*	*Total* score*	*MVA-pre echo*	*MVA-post echo*
1	67	M	SR	IV	0·7	2·5	20	4	42	25	50	40	Sub	14	0·5	1·8
2	71	M	AF	III	0·7	1·5	12	8	22	19	52	38	Sub	10	1·2	†
3	72	F	AF	III	0·9	1·7	9	5	15	10	21	18	Opt	6	1·8	2·4
4	57	F	SR	III	1·6	2·9	15	6	15	10	25	20	Opt	9	1·4	2·0
5	56	F	SR	III	1·0	2·2	18	5	25	5	34	14	Opt	7	0·9	1·6
6	49	F	AF	III	0·8	1·5	9	5	17	18	31	35	Sub	9	1·0	1·5
7	40	F	SR	II	0·7	2·0	30	6	38	10	75	35	Opt	5	1·0	2·1
8	42	F	SR	III	1·1	1·3	28	14	32	18	40	25	Sub	9	1·0	1·5
9	59	F	SR	IV	0·4	1·6	22	2	20	10	48	15	Opt	11	0·4	1·4
10	40	F	SR	III	1·0	2·3	25	5	30	7	40	25	Opt	5	0·8	2·0
11	88	F	AF	IV	0·5	1·0	15	4	35	20	52	35	Sub	14	0·8	1·6
12	27	F	SR	III	0·7	2·8	24	4	30	8	42	18	Opt	7	0·7	2·4
13	71	F	AF	IV	0·5	1·2	18	5	22	17	53	40	Sub	16	†	†
14	47	F	SR	III	0·8	2·1	20	7	32	10	40	28	Opt	5	1·1	2·1
15	68	F	AF	IV	0·7	0·8	9	8	20	12	50	40	Sub	10	0·8	0·8
16	64	F	AF	III	0·6	1·5	12	5	18	10	45	35	Opt	11	0·8	1·1
17	72	F	SR	IV	0·9	1·7	17	4	21	22	30	†	Sub	10	0·9	1·7
18	21	M	SR	III	0·6	1·8	15	3	22	6	35	20	Opt	4	0·6	1·8
19	78	F	AF	IV	0·4	‡	20	‡	35	‡	40	‡	Sub	12	0·4	‡
20	51	M	SR	III	0·6	2·1	25	5	25	5	36	25	Opt	10	0·5	2·3
21	53	F	AF	III	1·4	1·6	16	12	21	12	32	17	Sub	11	1·4	1·6
22	54	F	SR	IV	0·5	0·9	31	11	39	12	62	29	Sub	11	1·1	1·2

SR, sinus rhythm, AF, atrial fibrillation; NYHA, New York Heart Association functional class; MVA-pre and MVA-post, Gorlin mitral valve area before an after balloon dilatation; Grad pre and Grad post, mean transmitral gradient before and after balloon dilatation; Pre LA-P and post LA-P, mean left atria pressure before and after balloon dilatation; PA pre and PA post, mean pulmonary artery pressure before and after balloon dilatation, MVA-pre and MVA- post, echocardiographic mitral valve area before and after balloon dilatation; *total echocardiographic score; †Technically limited measurements ‡Measurements not performed because of acute haemodynamic deterioration.

CLINICAL FEATURES

Of the 22 patients, 13 were in sinus rhythm and 9 were in atrial fibrillation. By the New York Heart Association functional class, one (5%) patient was in class II, 13 (59%) were in class III, and 8 (36%) were in class IV.

ECHOCARDIOGRAPHIC FEATURES

Each patient was studied by cross sectional and Doppler echocardiography before the procedure. Most studies (20 of 22, 91%) were performed within 24 hours of the procedure; the remaining two studies were performed within three months. To analyse the effect of mitral valve structure on the results of dilatation, we scored the echocardiographic study of each patient for: (*a*) leaflet mobility, (*b*) leaflet thickening, (*c*) subvalvar thickening, and (*d*) calcification. Table 2 shows the scoring system. We gave each of the above features a score of 0–4, and higher scores represented more abnormal structure. For example, for mobility, grade 1 was a highly mobile valve with restriction of only the leaflet tips. Grade 4 indicated a valve that was almost completely immobile with no (or minimal) forward movement

Table 2 *Grading of mitral valve characteristics from the echocardiographic examination*

Grade	*Mobility*	*Subvalvar thickening*	*Thickening*	*Calcification*
1	Highly mobile valve with only leaflet tips restricted	Minimal thickening just below the mitral leaflets	Leaflets near normal in thickness (4–5 mm)	A single area of increased echo brightness
2	Leaflet mid and base portions have normal mobility	Thickening of chordal structures extending up to one third of the chordal length	Mid-leaflets normal, considerable thickening of margins (5–8 mm)	Scattered areas of brightness confined to leaflet margins
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending to the distal third of the chords	Thickening extending through the entire leaflet (5–8 mm)	Brightness extending into the mid-portion of the leaflets
4	No or minimal forward movement of the leaflets in diastole	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles	Considerable thickening of all leaflet tissue (>8–10 mm)	Extensive brightness throughout much of the leaflet tissue

The total echocardiographic score was derived from an analysis of mitral leaflet mobility, valvar and subvalvar thickening, and calcification which were graded from 0 to 4 according to the above criteria. This gave a total score of 0 to 16.

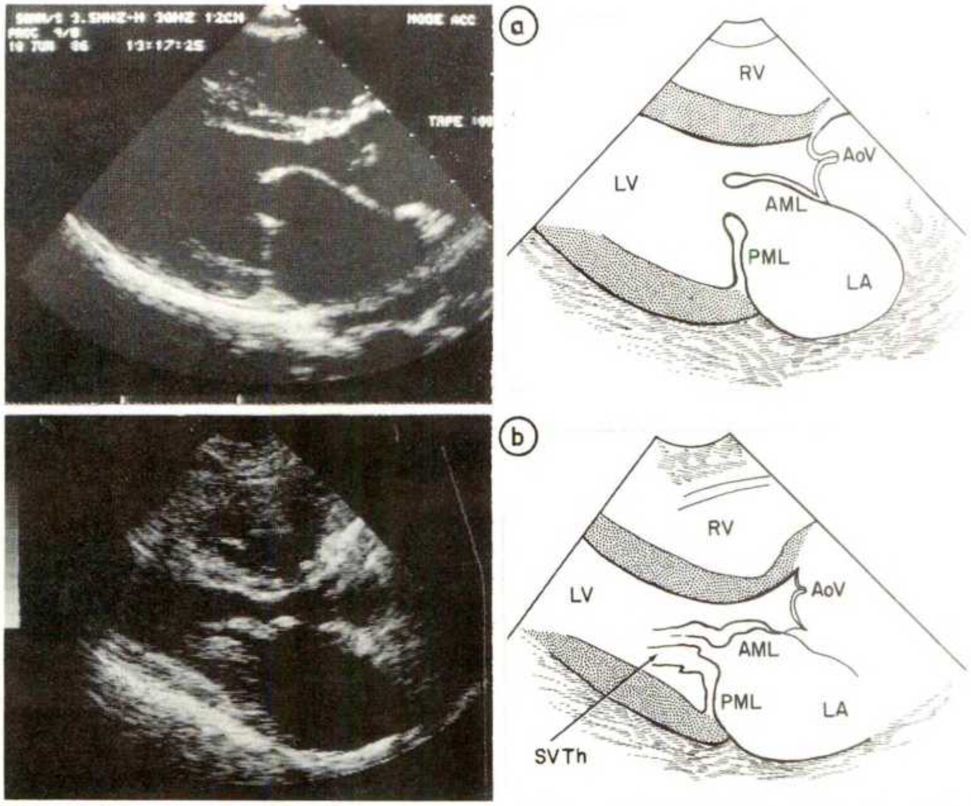

Fig 1 *(a) Echocardiographic parasternal long axis view showing a highly mobile, "doming" anterior (AML) and posterior (PML) mitral valve with slightly thickened leaflet tips. There is no evidence of subvalvar thickening. The echo score is 4. (b) The mitral leaflets are thickened and this thickening (SVTh) extends below the leaflet tips into the subvalvar apparatus. The echo score is 11.*

during diastole (figs 1 and 2). Summing the individual scores resulted in a total echocardiographic score. According to this system, a score of 0 would be a totally normal valve (no such valve was included in this series), while a score of 16 would represent an immobile valve with considerable thickening of the leaflets and subvalvar apparatus and severe superimposed calcification.

Subvalvar thickening was best displayed by a series of modified views. In the parasternal long axis view, the standard aligned view was tilted medially and laterally so that the long axis of each papillary muscle and its attached chordal apparatus could be examined in turn. From the apical window, the extent of subvalvar shortening and scar was best viewed in a four chamber view with the transducer angled more posteriorly into the left ventricle, or from a foreshortened two chamber view angled medially and laterally.

The left atrial volume was calculated from the echocardiographic images before and after the procedure by an ellipsoid formula, in which the length was taken as the superior-inferior length of the atrium in the apical four chamber view and the two diameters used were the anterior-posterior and medial-lateral dimensions measured in the parasternal long and short axis views respectively (fig 3). The anterior-posterior diameter (D1, fig 3a) and the superior-inferior length (D3, fig 3c) were measured in the frame obtained immediately before mitral valve opening. The medial-lateral diameter (D2, fig 3b) was measured in a view in which the mitral valve cannot be seen in the frame during which aortic valve closure was completed. Mitral valve area was measured by direct planimetry in the standard manner[16 17] before and within 24 hours of the procedure (fig 4). Technically satisfactory images of the mitral valve orifice suitable for planimetry could not be obtained either before or after the procedure in one patient and after the procedure in another (patients 13 and 2 respectively, table 1). The presence and extent of mitral regurgitation were also mapped

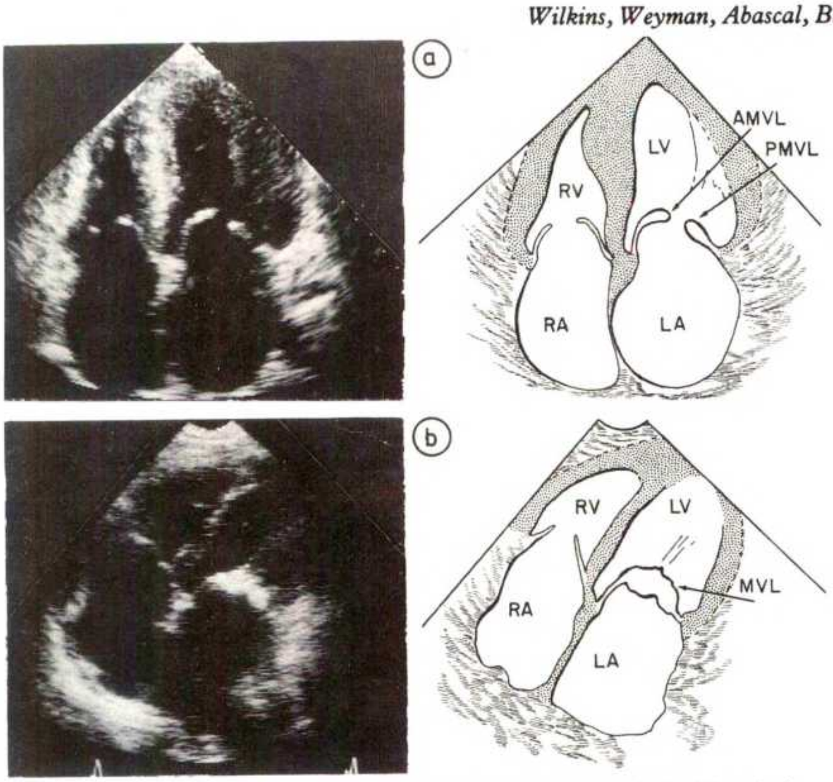

Fig 2 *(a) Echocardiographic apical four chamber view showing "doming" of the mitral valve with slight thickening of the anterior (AMVL) and posterior (PMVL) leaflet tips. The echo score is 4. (b) Extensive thickening of the leaflets (MVL) and a considerable increase in echo density suggesting the presence of calcification. The echo score is 14.*

before and after the procedure by the pulsed Doppler technique in order to assess any adverse effect of this variable on outcome.[18] Mitral regurgitation was graded on a scale of 1 to 4+ by dividing the atrium into four equal segments along its long axis and constructing an arc centred at the mid-point of the mitral valve that extended from the end of each quadrisecting point to the medial and lateral walls of the atrium. High velocity systolic flow was then graded according to its penetration into these segments. Grade 4 represented flow detected at the most superior atrial segment.

HAEMODYNAMIC VARIABLES

Each patient was catheterised from the right femoral approach. The interatrial septum was first crossed by the Brockenborough technique. A flow directed catheter was then passed through the transseptal sheath and, together with a flexible exchange guide wire, advanced through the mitral valve orifice. Left atrial and left ventricular pressures were measured, and the mean transmitral pressure difference was calculated. Pulmonary artery pressure was measured with a Swan-Ganz catheter inserted via the internal jugular vein. Cardiac output was measured by thermodilution, Fick, or green dye dilution techniques. We calculated the mitral valve area by the Gorlin equation.[19]

After these haemodynamic measurements, percutaneous balloon dilatation of the mitral valve was performed by either a single or double balloon dilating technique.[7] A single balloon procedure was performed in 17 patients: a single 15 mm balloon in one, a single 20 mm balloon in one, and a single 25 mm balloon in 15 patients. In four patients a double balloon procedure was performed with a combination of a 25 mm and 15 mm balloon. Once the catheter(s) was positioned across the orifice, the balloon(s) was inflated by hand until the indentation caused by the stenotic mitral valve disappeared. Each inflation lasted approximately 15 seconds and multiple inflations were performed in all patients. In one patient (patient 19, table 1) the valve could not be crossed with an 8 mm balloon catheter, and the patient became profoundly hypotensive. Mitral valve replacement was uneventful, but the patient could not be weaned from cardiopulmonary bypass because of profound right heart failure and she died.

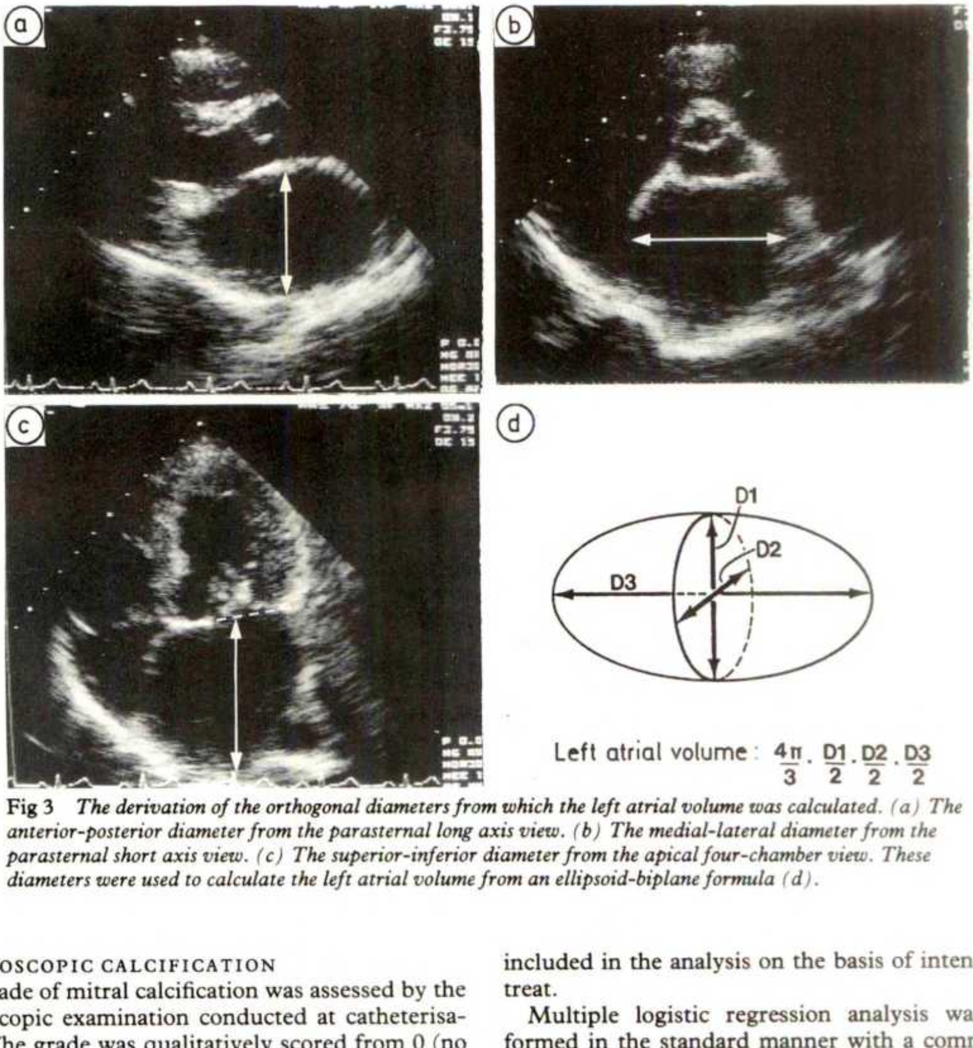
a
b
c
d
D1
D2
D3
Left atrial volume : $\frac{4\pi}{3} \cdot \frac{D1}{2} \cdot \frac{D2}{2} \cdot \frac{D3}{2}$

Fig 3 *The derivation of the orthogonal diameters from which the left atrial volume was calculated. (a) The anterior-posterior diameter from the parasternal long axis view. (b) The medial-lateral diameter from the parasternal short axis view. (c) The superior-inferior diameter from the apical four-chamber view. These diameters were used to calculate the left atrial volume from an ellipsoid-biplane formula (d).*

FLUOROSCOPIC CALCIFICATION

The grade of mitral calcification was assessed by the fluoroscopic examination conducted at catheterisation. The grade was qualitatively scored from 0 (no calcification seen) to 4 (severe calcification).

STATISTICAL ANALYSIS

To determine whether any variable or combination of variables predicted a successful outcome of balloon dilatation, all echocardiographic, Doppler, haemodynamic, and clinical data were analysed by multiple logistic regression analysis. The dependent variable was either an optimal or a suboptimal result. A suboptimal result was defined as any one or more of the following: (*a*) a final valve area $\leqslant 1 \cdot 0$ cm^2, (*b*) a post-dilatation mean left atrial pressure > 10 mm Hg, or (*c*) a change in area $< 25\%$ of the initial valve area in those with a mitral valve area $> 1 \cdot 0$ cm^2 before the procedure.

One patient (case 19, table 1) who died soon after attempted percutaneous mitral balloon dilatation was included in the analysis on the basis of intention to treat.

Multiple logistic regression analysis was performed in the standard manner with a commercial statistical package, BMDP.[20] Data are presented as mean (1 SD). The outcome in the subgroups (optimal *v* suboptimal) was compared by the unpaired Student's *t* test for parametric data or the Wilcoxon signed rank test for non-parametric data. The frequency of events was compared by the χ^2 or Fisher's exact test. Interobserver variability was determined from the mean unsigned differences between two sets of measurements performed blindly by two experienced observers. Intraobserver variability was determined in the same way from two sets of measurements performed by the same observer on different days.

Results

Table 1 shows the clinical, echocardiographic, and

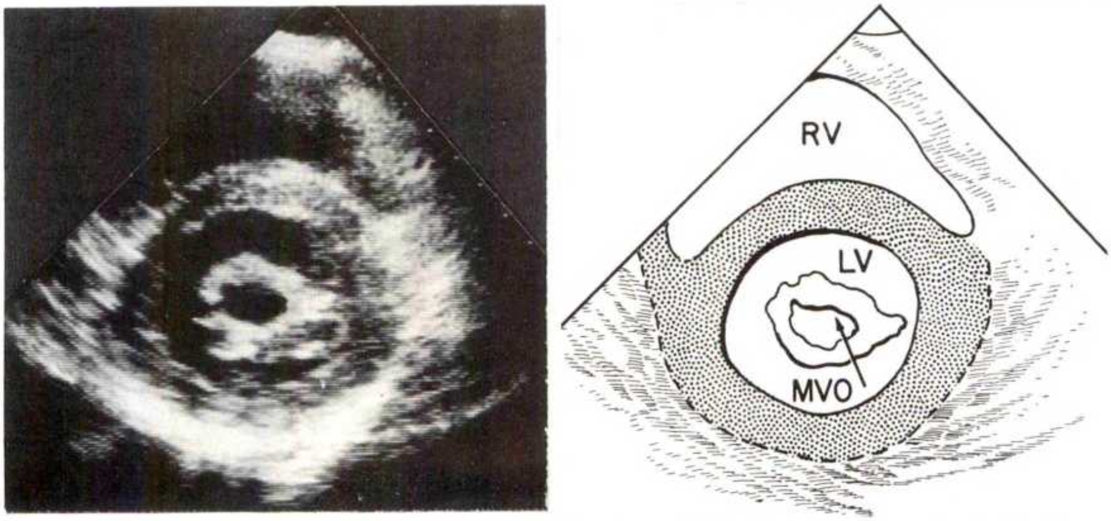

Fig 4 *An echocardiographic parasternal short axis view of the mitral valve orifice in diastole (patient 16, table 1). The small central orifice (MVO) is surrounded by the circular outline of the left ventricular cavity. The margins of the central orifice were electronically traced and the mitral valve area (0·6 cm^2) was calculated by planimetry.*

haemodynamic variables for each patient.

The mean valve area measured by planimetry of the cross sectional echocardiographic short axis images before balloon dilatation was 0·9 (0·46) cm^2 (range 0·40–1·8 cm^2). After dilatation, the mean area increased to 1·7 (0·45) cm^2 (range 0·81–2·4 cm^2, $p < 0{\cdot}0001$). The individual increases in valve area varied considerably, and ranged from 0·1 to 1·81 cm^2.

The mean valve area measured by the catheterisation method (Gorlin equation) before balloon dilatation was 0·8 (0·30) cm^2 (range 0·4–1·6 cm^2). After balloon dilatation, the mean area increased to 1·76 (0·6) cm^2 (range 0·8–2·9 cm^2, $p < 0{\cdot}0001$). Changes in valve area measured by the planimetry method and by the Gorlin equation were strongly correlated ($r = 0{\cdot}9$, $p < 0{\cdot}001$).

Table 1 shows total echocardiographic score for leaflet mobility, leaflet thickening, leaflet calcification, and subvalvar thickening for each patient before balloon dilatation. On a scale of 0 to 16, representing increasing structural deformity, the severity ranged widely from 4 to 16 (mean grade 9·4 (3·1)). In 12 randomly selected cases, the mean interobserver variability for the total echocardiographic score was 0·41 (0·51). The intraobserver variability for the echocardiographic score in the same patients was 0·38 (0·4).

The mean grade of regurgitation by Doppler was 1·0 (1·2) with a range of 0 to 3. After dilatation, the mean grade of regurgitation increased to 1·8 (1·1) and ranged from 0 to 3. Although this increase in the degree of regurgitation (by Doppler) represented a significant increase ($p < 0{\cdot}01$), no patient developed grade 4 regurgitation. Mean left atrial volume was 95 (47) cm^3 (range 52–220 cm^3), which was significantly larger than the normal values of 32 (10) cm^3 previously reported from our laboratory.[21] After dilatation the mean left atrial volume decreased significantly to 83 (12) cm^3 ($p < 0{\cdot}001$).

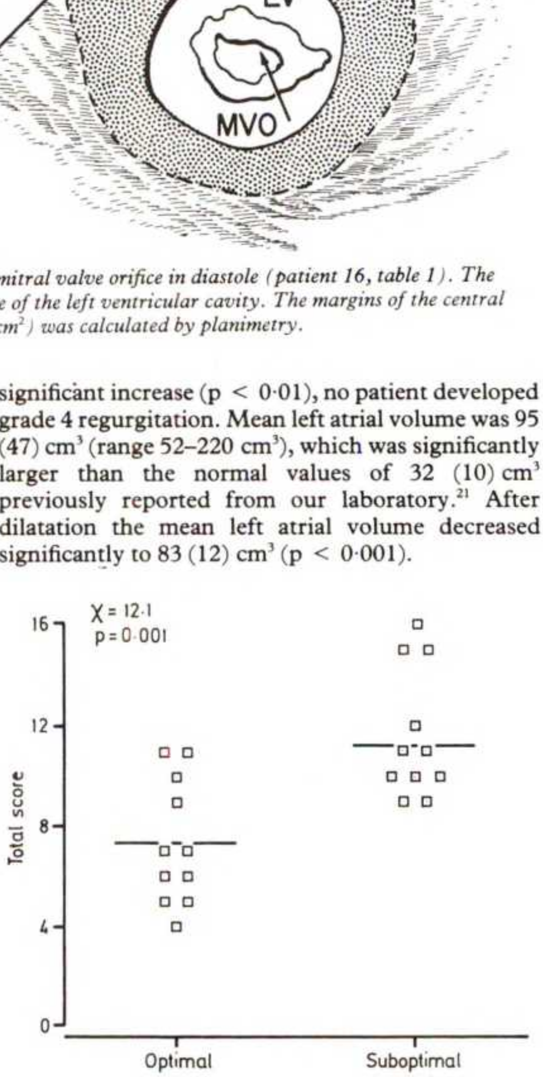

Fig 5 *Total echocardiographic score for each patient (from 0 to 16) in patients grouped according to outcome. The bar shows mean total score for each group. Logistic regression analysis according to outcome selected the total echocardiographic score alone as the best predictor.*

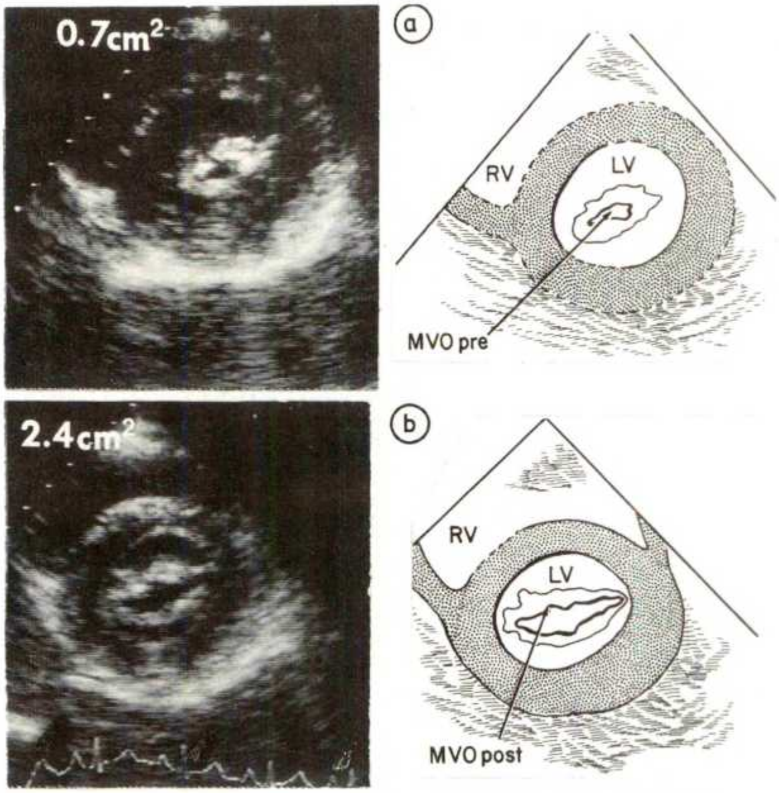

Fig 6 *Cross sectional echocardiographic images from study patient 12 (table 1) immediately before and 24 hours after balloon dilatation of the mitral valve. (a) The small central orifice (0·7 cm²) (MVO pre). After the procedure, the orifice (MVO post) was significantly larger (2·4 cm²) (b) with cleavage along the medial and lateral commissures which had previously appeared as dense scarred regions.*

The mean grade of calcification (by fluoroscopy) was 1·4 (1·5) and ranged from grade 0 to 4. Ten patients had no obvious calcification of the leaflets by fluoroscopic examination and only one had grade 4 calcification.

The haemodynamic data showed a mean transmitral pressure difference of 18·6 (6·6) mm Hg, mean cardiac output of 3·9 (1·2 l/min), mean pulmonary vascular resistance of 384 (289) dynes.s. cm^{-5}, and a mean left ventricular end diastolic pressure of 8 (3) mm Hg.

The mean dilating area of the balloon(s) was 4·89 cm² (approximately equal to a single 25 French balloon).

ANALYSIS FOR PREDICTORS OF AN OPTIMAL OR SUBOPTIMAL RESULT

There were 11 patients with an optimal result and 11 patients with a suboptimal result (see Methods section for criteria).

Comparison of the mitral valve structure in the groups with optimal and suboptimal outcome showed significant differences in the degrees of valve mobility (mean optimal group 1·8 (0·96) and mean suboptimal group 3·18 (0·75), p < 0·001), valve thickening (mean optimal group 2·1 (0·8) and mean suboptimal group 3·2 (0·6), p < 0·001), subvalvar thickening (mean optimal group 1·7 (0·6) and mean suboptimal group 2·5 (0·8), p < 0·01), and valve calcification (mean optimal group 1·8 (0·9) and mean suboptimal group 2·6 (0·8) p < 0·03). The total echocardiographic score was also significantly different in the two groups (mean optimal group 7·36 (2·5) (range 4–11) and suboptimal group 11·5 (2·3) (range 9–16), p < 0·001), with an optimal outcome associated with a lower score (fig 5).

Analysis of the clinical variables showed that the mean New York Heart Association functional class was lower (optimal 3·0 (0·4) and suboptimal 3·63 (0·5), p = 0·005) and the mean fluoroscopic grade of calcification was lower (mean optimal grade 0·5 (1·0) and mean suboptimal grade 2·3 (1·4), p = 0·003) in the optimal result group. The frequency of sinus rhythm or atrial fibrillation was not significantly different in the groups with optimal and suboptimal outcome, although there was a trend towards a higher occurrence of sinus rhythm in the optimal outcome group ($p = 0{\cdot}08$). No difference was found in the sex distribution of the two groups.

For the remaining variables the two outcome groups showed no difference in initial left atrial volume, initial valve area, or the Doppler grade of mitral regurgitation. The effective balloon dilating area used was not different (although there was a trend towards an optimal result with larger effective balloon areas such as those previously reported[7]). The order in which the patients had their intervention performed was analysed to determine whether a learning curve affected outcome; this showed no difference between the two groups in mean position within the series. No difference was noted between the two groups for the initial transmitral gradient, cardiac output, or pulmonary artery pressure and resistance.

MULTIPLE LOGISTIC REGRESSION ANALYSIS FOR THE MAJOR PREDICTOR(S) OF OUTCOME

When multiple logistic regression analysis was performed with the outcome as the dependent variable (optimal *v* suboptimal), the total echocardiographic score on its own was found to be the best predictor (multiple $\chi^2 = 12{\cdot}1$, $p < 0{\cdot}0001$). The fit of the logistic regression was not improved by the addition of any other variable. Figure 5 shows the individual total echocardiographic scores for each patient and the outcome group to which each individual belongs. Although four patients with relatively high scores (that is significant immobility, thickening, and subvalvar thickening) had an optimal result. In general, however, the analysis suggested that a high score was associated with a suboptimal outcome.

ANALYSIS FOR THE MECHANISM OF DILATATION

Careful examination of the short axis echocardiographic images showed that successful balloon dilatation of the mitral valve was associated with cleavage along the commissures (fig 6). This appearance occurred even in those patients who had significantly thickened and calcified valve leaflets, although the degree of cleavage was less. Balloon dilatation in some patients with high total echocardiographic scores seemed to produce extensive commissural splitting, but, despite this, the separation of the leaflets in diastole remained poor. So the orifice area failed to increase relative to the increase in circumference, presumably because the deformed leaflets were unable to assume a more circular shape.

Discussion

This study shows that the outcome of percutaneous balloon dilatation of the mitral valve is most closely associated with echocardiographic characteristics of mitral valve structure. The mean values for the optimal and suboptimal outcome groups showed that there were significant differences in the degree of leaflet mobility, valvar and subvalvar thickening, and valve calcification between the two groups. For each of these variables, the greater the degree of leaflet deformity, the greater was the likelihood of a suboptimal outcome, and, conversely, valves with a more normal structure tended to be associated with an optimal outcome (fig 5). This observation, that the structure of the mitral apparatus is a major determinant of outcome in balloon dilatation of the mitral valve, is consistent with previous experience with surgical valvotomy. As early as 1953, Sellors *et al* suggested that the type of mitral stenosis was the major determinant of the success of closed surgical commissurotomy.[11] Their careful analysis of the physical signs related to a "pliant diaphragmatic valve" is the clinical forerunner of our own echocardiographic observations on leaflet mobility. Subsequent studies have confirmed that the mobility of the valve leaflets determined at operation[12] and the degree of fibrosis and calcification,[13-15] are the major determinants of both the short term and long term results of closed mitral commissurotomy. Indeed, the poor results obtained in those patients with evidence of advanced valvar and subvalvar disease have led to the common practice of open mitral commissurotomy on cardiopulmonary bypass, when the leaflets can be more directly inspected and incised.[13]

Although the primary structural feature that determines the haemodynamic severity of mitral stenosis is the mitral valve orifice area, the size of the orifice was in no way predictive of the outcome. Patients with small initial valve areas over the range studied were just as likely to have an optimal result as those with larger valve areas before the procedure. This finding is somewhat surprising since we would have expected the valve with the smallest areas to have the most associated deformity and thus a poorer result. This finding may relate to the highly selected patient group, since only those with critical disease were initially felt to be suitable for this new procedure. Since most valve areas were in the range of $0{\cdot}4$–$1{\cdot}0$ cm^2 it might be difficult reliably to separate out the effects of initial valve area upon the outcome. This consideration is important, however, because our results suggest that this procedure may be applied to patients with less severe mitral stenosis (larger valve areas) and at an earlier stage in the natural history of their disease, when the leaflets are less thickened and more mobile. As this group increases, valve area may also prove to be a predictor of outcome.

Several clinical factors, other than the echocardiographic variables, were also related to an optimal outcome. These factors were the presence of a lower New York Heart Association functional class, and a lower fluoroscopic grade of calcification. The initial haemodynamic variables that we measured (pre-dilatation transmitral gradient, cardiac output, and pulmonary artery pressure and resistance) were not related to immediate outcome in this group of patients. These findings are also consistent with previous surgical results after commissurotomy.[12-15]

A simple comparison of mean values in our study shows that both echocardiographic and clinical factors distinguished between the optimal and suboptimal outcome groups. Since this analysis does not determine the most important variable or combination of variables that may predict outcome, a multiple logistic regression analysis was performed to weigh the significance of each of these factors. This approach showed the single most important factor that could be related to outcome was the total echocardiographic score, which expressed the combined assessment of leaflet mobility, valvar and subvalvar thickening, and leaflet calcification. With this score we were able to assess differing degrees of leaflet immobility, deformity, and scarring. All patients with a total echocardiographic score >11 had a suboptimal result while all those with a score <9 had an optimal result. The score failed to predict outcome in those with scores of 9 to 11 (fig 5). Of the echocardiographic variables, no single factor, such as subvalvar thickening or valvar mobility alone, could be separated from the other structural features as a significant determinant of outcome. The addition of haemodynamic or clinical variables or both, individually or in combination, also failed to improve the logistic fit. Thus although outcome in this group of patients is associated both with echocardiographic and clinical variables it is best predicted by the echocardiographic score alone.

The effective dilating area of the balloon was not a significant predictor of outcome. Clearly, a much greater dilating area can be achieved with the use of a double balloon technique, such as that described by Al Zaibag *et al*[4] and Palacios *et al*.[7] This series, representing our earlier experience, contains only four patients in whom we used a double balloon technique. Nevertheless, we saw a trend towards a better result. We therefore believe that the effective dilating area of the balloon would have emerged as a significant determinant of outcome[7] had more patients with a double balloon procedure been included in the analysis.

Finally, balloon dilatation of the mitral valve seemed reliably to result in splitting of the mitral commissures and not in traumatic avulsion or damage to the leaflet bodies. Since the inflation of a fluid-filled balloon within the confines of a small orifice results in equal pressure being applied to all points on the surface, separation of the valve along the plane of least resistance (that is the commissures) is to be expected (fig 6).

LIMITATIONS OF THE STUDY

The echocardiographic analysis presented in this report is based on a qualitative assessment of the mitral valve and apparatus. Although a more objective method of assessment may be desirable, it should be remembered that when surgeons or pathologists are able to handle the mitral valve they still describe any structural deformities in a qualitative manner because there are no accepted objective measures of mobility, thickening, or subvalvar thickening. Indeed it could be argued that because cross sectional echocardiography provides an assessment of these features (particularly mobility) in the beating heart it is better than examination during cardiopulmonary bypass or at necropsy. The simplicity of the approach that we have described should make it a practical clinical method of assessing patients before balloon dilatation of the mitral valve.

With a qualitative method there may be differences between observers in the assessment of the degree of mitral mobility, valvar and subvalvar thickening, and valve calcification. None the less, the interobserver and intraobserver variability for experienced observers was acceptably low. The accuracy of the assessment of structure also depends on the quality of the echocardiographic images obtained. The pathophysiology of mitral stenosis, with secondary right ventricular and biatrial enlargement, facilitates echocardiographic imaging and visualisation of the mitral valve. Moreover, none of the patients in our series was excluded because we could not adequately assess mitral valve structure by echocardiography.

CONCLUSION

This study shows that the outcome of percutaneous balloon dilatation of the mitral valve is related to the structure of the mitral valve and the subvalvar apparatus. Simple criteria obtained non-invasively can predict the likelihood of success of the procedure and hence may be used to select suitable patients. Since the most favourable early results were seen in patients with the least advanced valve deformity and scarring, this study implies that the procedure is most successful in this group and should be performed before advanced scarring and immobility have occurred.

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Long term doxorubicin cardiotoxicity in childhood: non-invasive evaluation of the contractile state and diastolic filling

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SUMMARY Cardiac performance was evaluated at least two years after doxorubicin treatment in childhood in 55 patients without overt congestive cardiomyopathy. None of the patients had received mediastinal irradiation. Computer-assisted analysis of digitised echocardiograms showed impaired rapid diastolic filling and an increased change of dimension between minimal cavity dimension and mitral valve opening. This impairment of diastolic function was related to the cumulative dose of doxorubicin. In contrast when angiotensin II was infused to increase the afterload the end systolic pressure-length and stress-shortening relation indicated normal left ventricular systolic function. But during baseline conditions the end systolic wall stress was significantly increased in patients in whom the cumulative dose of doxorubicin exceeded 360 mg/m^2.

Doxorubicin is a highly effective antineoplastic agent, but its use is limited by a cumulative dose-related cardiomyopathy.[1] There is still considerable concern about long term cardiac performance after antineoplastic treatment with doxorubicin, particularly in childhood.[2-4] The cumulative dose of doxorubicin should be limited to 450 mg/m^2 body surface area.[1] But some patients develop cardiomyopathy even at lower cumulative doses, particularly when there are additional risk factors such as mediastinal irradiation.[1] Doxorubicin can cause specific ultrastructural changes in the myocardium at much lower cumulative doses, without altering left ventricular function.[5-7] This suggests that even relatively low cumulative doses of doxorubicin can cause subclinical damage.

The standard indices of left ventricular performance—the ejection phase indices—cannot discriminate between abnormal contractility and altered loading conditions (preload and afterload).[8-10] Although the extent of myocardial fibre shortening is often used as an index of contractility, it is really a reflection of the interaction between contractile state, preload, and afterload.[9-11] The slope of the end systolic pressure-length relation, however, is an index of the contractile state that is independent of load.[12-14] The end systolic stress-shortening relations seem to be even more sensitive measures of impaired contractility.[9-11]

Chronic anthracycline cardiotoxicity can alter diastolic function too. Recently Mortensen *et al* reported haemodynamic and structural findings suggestive of restrictive endomyocardial disease after treatment with anthracyclines.[15] Altered diastolic properties were also recognised by computer-assisted analyses of digitised echocardiograms.[16 17] These reports show that diastolic function must be studied when the effect of chronic doxorubicin cardiotoxicity is being examined.

We evaluated long term cardiac performance after doxorubicin treatment in childhood. We studied the contractile state by analysing the end systolic pressure-length and stress-shortening relations and we used computer-assisted analysis of digitised echocardiograms to evaluate diastolic filling.

Patients and methods

PATIENT GROUP

We studied 55 patients who had been treated with doxorubicin for childhood malignancies. In all

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patients doxorubicin was part of a multiple drug regimen (*leukaemia*: doxorubicin, vincristine, methylprednisolone, cyclophosphamide, 6-mercaptopurine, arabinoside-C; *osteosarcoma*: doxorubicin, methotrexate, bleomycin, actinomycin-D, cyclophosphamide; *Ewing's sarcoma and soft tissue sarcoma*: doxorubicin, vincristine, cyclophosphamide, actinomycin-D, bleomycin).

All patients were in complete remission after the end of antineoplastic treatment. None of them had been treated by irradiation of the mediastinum. The cumulative dose of doxorubicin ranged from 31 to 656 mg/m² (mean (SD) 273 (152) mg/m²). All patients had been off treatment for at least two years (range 2·1 to 10·4). We selected those who had been off treatment for the longest time from among patients who had had similar cumulative doses of doxorubicin. After five patients had been excluded from the study (see Results) patients were arbitrarily divided into three groups according to their cumulative dose of doxorubicin: *group 1* (n=20), <180 mg/m²; *group 2* (n=13), 180–360 mg/m²; *group 3* (n=17), >360 mg/m².

CONTROL GROUP

The control group consisted of 30 healthy volunteers aged 18–30.[8] None had a history of cardiovascular disease. Physical examination, electrocardiography, M mode echocardiography, and cross sectional echocardiography showed no abnormalities. None of them was taking medications.

ECHOCARDIOGRAMS

Echocardiograms were performed with Picker 80C Echoview ultrasound imaging device with a 3·5 MHz and 2·25 MHz transducer. The M mode echocardiograms were recorded at the tip of the mitral valve leaflets in the standard position at a paper speed of 100 mm/s.[18] The transducer was held in position for all measurements. All echocardiograms were recorded by one echocardiographer to eliminate interobserver variability. A carotid pulse tracing was recorded simultaneously with the M mode echocardiogram. It was corrected for pulse transmission delay by aligning it with the aortic valve echocardiogram.

EVALUATION OF THE CONTRACTILE STATE

Measurement of end systolic pressure

Systolic and diastolic blood pressure were measured by a Dinamap 845 Vital Signs Monitor (Criticon Inc.). This device has been shown to estimate central aortic pressure accurately over a wide range of pressure and independently of cardiac index, systemic vascular resistance, heart rate, and body surface area.[19] The end systolic pressure (P_{es}) was estimated by the method of Stefadouros *et al*[20] by linear interpolation of the height of the dicrotic notch of the indirect carotid pulse tracing.[19 20]

Study protocol

All examinations were performed in patients resting in the semisupine position. The patients relaxed for at least 10 minutes before the examination. Intravenous atropine (0·01 mg/kg) was given before the examination, to reduce reflex cardiac slowing.[8] After baseline recordings the blood pressure was slowly increased by the infusion of angiotensin II (0·5–3·5 μg/min). We attempted to increase systolic blood pressure to 30 mm Hg above baseline values. During the increase in blood pressure we made several simultaneous recordings of the M mode echocardiogram, carotid pulse tracing, and arterial blood pressure. We obtained the informed consent of all patients or their parents. The study protocol was approved by the local committee for human research.

Measurements and calculation

We took the mean of three consecutive cardiac cycles. Data points were excluded when the heart rate varied by more than 10 beats per minute from baseline values.[8–10] The end diastolic internal left ventricular dimension (D_{ed}) was measured at the start of the QRS complex of the electrocardiogram and the end systolic left ventricular dimension (D_{es}) and posterior wall thickness (PW_{es}) were measured at end ejection (assessed from the time corrected carotid pulse tracings). Ejection time (ET) was measured from the carotid pulse tracing. The end diastolic left ventricular dimension was corrected for differences of body surface area (BSA) according to[21]:

$$D_{ed\,(corr)} = D_{ed} \times (BSA)^{-1/3}.$$

Fractional shortening (FS) was calculated as:

$$FS = \frac{D_{ed} - D_{es}}{D_{ed}} \times 100\%.$$

Mean fibre shortening velocity (VCF_{mean}) as:

$$VCF_{mean} = (FS/ET) \times 10\,s^{-1}.$$

End systolic meridional wall stress (σ_{es}) was calculated according to the method of Brodie *et al*[22]:

$$\sigma_{es} = 1{\cdot}35 \times \frac{PW_{es} \times D_{es}}{4 \times PW_{es} \times (1 + PW_{es}/D_{es})}\ (g/cm^2).$$

The slopes a_1 to a_3 of the relations between end systolic pressure and dimension ($P_{es} - D_{es}$ relation), end systolic wall stress and fractional shortening (σ_{es} − FS relation), and end systolic wall stress and mean fibre shortening velocity (σ_{es} − VCF relation) were calculated according to the following equations:

$P_{es} - D_{es}$ relation: $P_{es} = a_1 \times D_{es} + b$

σ_{es} − FS relation: $FS = a_2 \times \sigma_{es} + b$

σ_{es} − VCF relation: $VCF = a_3 \times \sigma_{es} + b$

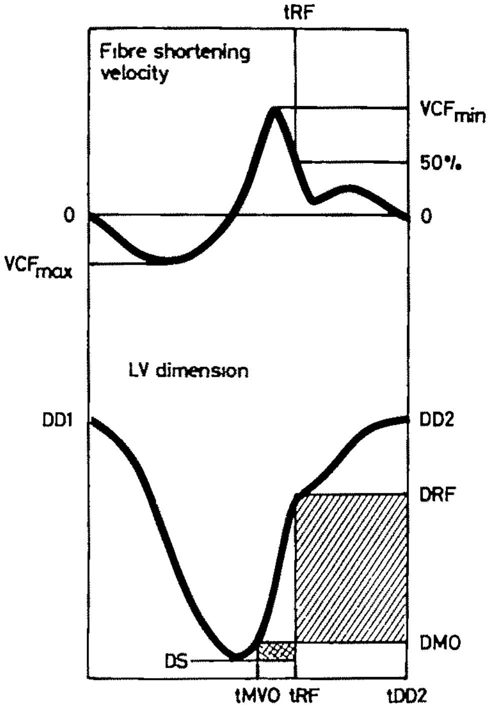

Fig 1 *The instantanous left ventricular (LV) internal dimension (lower curve) and its first derivative, the fibre shortening velocity (upper curve). DD1, end diastolic dimension at the beginning of the cardiac cycle; DD2, end diastolic dimension at the end of the cardiac cycle; DS, minimal left ventricular dimension; DMO, dimension at mitral valve opening; DRF, dimension at the end of rapid diastolic filling (point at which the normalised fibre shortening velocity had decreased to 50% of its peak value); tMO, time of mitral valve opening; tRF, time of the end of rapid diastolic filling; tDD2, end of cardiac cycle;* VCF_{max}, *maximal fibre shortening velocity;* VCF_{min}, *minimal fibre shortening velocity or maximal fibre lengthening rate.*

EVALUATION OF DIASTOLIC FUNCTION

Computed-assisted analyses

We used only good quality echocardiograms for computer-assisted analysis. The M mode echocardiograms were manually digitised with a Cardio 200 computer (Kontron Image Analysis). Three consecutive cardiac cycles were analysed and the mean was used for further calculations. The following were measured:

Measurement of time intervals—Time intervals were measured from the beginning of the Q wave. The interval between minimal cavity dimension and mitral valve opening (tDS-MO) was measured from the point at which the fibre shortening velocity curve crossed zero to the time of mitral leaflet separation (fig 1).[23 24]

Measurement of dimensions and changes in dimension—The end diastolic left ventricular dimension (DD) was measured at the beginning of the first Q wave of the cardiac cycle being analysed. Left ventricular dimension at aortic valve closure was taken as the end systolic dimension (D_{a}). The maximal normalised fibre lengthening rate (VLR_{max}) was measured as the maximum of the first derivative of the left ventricular internal dimension curve that was standardised according to the instantaneous left ventricular dimension.[23] Minimal cavity dimension (DS) was measured at the point where the first derivative of the instantaneous left ventricular dimension curve crossed zero.

The change of dimension between minimal cavity dimension and mitral valve opening was defined as[23 24]:

$$dDS - MO = \frac{DMO - DS}{DD2 - DS} \times 100\%$$

where DMO is the dimension at mitral valve opening; DS, minimal cavity dimension; and DD2, end diastolic dimension at the end of the cardiac cycle.

The end of rapid diastolic filling was defined as that point where the fibre shortening velocity had decreased to 50% of its peak value (fig 1).[25] The change of dimension with rapid diastolic filling (dRF) was calculated as:

$$dRF = \frac{DRF - DMO}{DD2 - DMO} \times 100\%$$

where DRF is the dimension at the end of rapid diastolic filling; DS, minimal cavity dimension; DMO, dimension at mitral valve opening; and DD2 end diastolic dimension at the end of the cardiac cycle.

STATISTICAL ANALYSIS

Linear regression analysis was performed to calculate the slope values of the individual relations between end systolic pressure and dimension, end systolic wall stress and fractional shortening, and end systolic wall stress and mean velocity of fibre shortening. At least five data points were available in all patients and controls. The three patient groups and the control group were compared by analysis of variance with the SAS-program and the differences between two groups were tested by Duncan's multiple range test.

To eliminate the influence of different ages (and so differences of body surface area and heart rate) and different time intervals between end of treatment and investigation, analysis of covariance was performed with the covariates "age at investigation" and "time interval between end of treatment and investigation"; differences between the adjusted means were tested by a t test matrix. A p value of < 0.05 was regarded as statistically significant.

Table 1 *Mean (SD) baseline haemodynamic function*

	Group 1	*Group 2*	*Group 3*	*Control*
Heart rate (beats/min)	81 (16)	76 (19)	74 (17)	63 (10)
D_{ed} (mm)	44 (4·4)	48 (7·6)	48 (5·5)	48 (3·5)
$D_{ed\,(corr)}$	40 (2·5)	40 (4·9)	40 (3·8)	40 (2·2)
P_{syst} (mm Hg)	116 (11)	125 (15)	117 (9)	121 (7)
P_{es} (mm Hg)	84 (12)	92 (18)	85 (11)	89 (9)
σ_{es} (g/cm^2)	49 (11)	56 (28)	59 (21)	50 (10)
FS (%)	34 (4·3)	34 (6·5)	31 (5·2)	34 (2·6)
VCF_{mean} (cm/s)	1·2 (0·20)	1·2 (0·24)	1·1 (0·19)	1·1 (0·12)

D_{ed}, end diastolic dimension; $D_{ed\,(corr)}$, end diastolic dimension corrected for differences in body surface area; P_{syst}, systolic arterial blood pressure, P_{es}, end systolic pressure, σ_{es}, end systolic meridional wall stress; FS, fractional shortening; VCF_{mean}, mean fibre shortening velocity

Results

PATIENT DATA

The mean (SD) age at the time of investigation was 16·7 (5·4) and the age at the end of antineoplastic treatment was 12·1 (4·9). The mean (SD) cumulative dose of doxorubicin was 273 (152) mg/m^2 (range 31–656 mg/m^2) (group 1, 120 (42) mg/m^2 (31–180 mg/m^2); group 2, 278 (74) (182–355 mg/m^2); group 3, 450 (70) mg/m^2 (363–656 mg/m^2). Five patients of the 55 patients had to be excluded from the study: one patient had an overt cardiomyopathy, two patients had raised blood pressure (in these three patients afterload challenge was not performed), and two patients had technically unsatisfactory echocardiograms.

BASELINE HAEMODYNAMIC FUNCTION

Table 1 shows the haemodynamic data at baseline conditions and table 2 shows the adjusted means according to analyses of covariance. Heart rates were significantly different in the various groups (analysis of variance $p<0·01$), but after adjustment of the means for the age at investigation, analysis of covariance showed no difference (table 2). The end diastolic left ventricular dimension was significantly different in the various groups (analysis of variance $p<0·03$); again, this was because of the age at the time of investigation (table 2) and the associated differences of the body surface area. After correction for body surface area ($D_{ed(corr)}$) the end systolic dimension was similar in all the groups (table 1).

The end systolic wall stress was significantly higher in patients with a cumulative dose of doxorubicin of >360 mg/m^2 (analysis of covariance $p<0·03$), whereas systolic, diastolic, mean, and end systolic arterial blood pressure were not significantly different in the various groups. No significant differences of fractional shortening and mean fibre shortening velocity were seen between the groups.

Table 2 *Baseline haemodynamic function (mean (SD)) with means adjusted for age at investigation and time since the end of antineoplastic treatment according to analysis of covariance*

	Group 1	*Group 2*	*Group 3*	*Control*
Heart rate (beats/min)	77 (3·7)	79 (4·3)	78 (4·0)	64 (8·0)
D_{ed}	45 (1·1)	46 (1·3)	47 (1·2)	48 (0·5)
σ_{es}	48 (3·6)	46 (4·3)	60 (3·9)	47 (5·9)
FS	34 (1·1)	36 (1·2)	31 (1·1)	34 (1·8)
VCF_{mean}	1·2 (0·04)	1·3 (0·05)	1·1 (0·05)	1·1 (0·10)

See footnote to table 1 for abbreviations.

Table 3 *Indices (mean (SD)) of left ventricular systolic performance*

	Group 1	*Group 2*	*Group 3*	*Control*
$P_{es}-D_{es}$	72·9 (24·9)	53·2 (19·9)	60·5 (23·1)	54·1 (18·4)
$\sigma_{es}-FS$	−0·204 (0·05)	−0·258 (0·05)	−0·216 (0·06)	−0·229 (0·04)
$\sigma_{es}-VCF$	−0·57 (0·27)	−0·84 (0·24)	−0·67 (0·26)	−0·66 (0·14)
Means adjusted for age at investigation and time since end of antineoplastic treatment according to analysis of covariance				
$P_{es}-D_{es}$	62·2 (5·4)	45·3 (4·9)	51·3 (5·3)	
$\sigma_{es}-FS$	−0·208 (0·014)	−0·257 (0·016)	−0·212 (0·015)	
$\sigma_{es}-VCF$	−0·62 (0·06)	−0·83 (0·07)	−0·62 (0·06)	

$P_{es}-D_{es}$, slope of the relation between end systolic left ventricular dimension and end systolic pressure; $\sigma_{es}-FS$, slope of the relation between end systolic wall stress and fractional shortening, $\sigma_{es}-VCF$, slope of the relation between end systolic wall stress and mean velocity of fibre shortening.

Table 4 *Indices (mean (SD)) of left ventricular diastolic function*

	Group 1	*Group 2*	*Group 3*	*Control*
dDS-MO (%)	4·7 (3·3)	10·8 (8·9)	16·7 (10·1)	7·4 (6·2)
dRF (%)	66·5 (13·7)	58·6 (17·5)	51·7 (18·9)	62·3 (6·2)
tDS-MO (ms)	42·1 (34·7)	58·5 (24·1)	66·5 (32·4)	34·9 (21·9)
VLR$_{max}$ (s^{-1})	3·86 (1·06)	3·46 (0·95)	3·03 (0·92)	4·10 (1·23)

dDS-MO, change of dimension between minimal cavity dimension and mitral valve opening; dRF, change of dimension with rapid diastolic filling; tDS-MO, time between minimal cavity dimension and mitral valve opening; VLR$_{max}$, maximal normalised fibre lengthening rate.

LEFT VENTRICULAR SYSTOLIC PERFORMANCE

The relations between end systolic pressure and dimension, end systolic wall stress and fractional shortening, and end systolic wall stress and mean fibre shortening velocity were linearly related in the normal subjects and patients, with linear regression coefficients ranging from 0·883 to 0·998. The slopes for these relations were not significantly different in the patient groups and the control group (table 3).

LEFT VENTRICULAR DIASTOLIC FUNCTION

The change of dimension in the interval between minimal dimension and mitral valve opening (dDS-MO) differed significantly between the groups (table 4) (analysis of variance $p < 0{\cdot}0001$, analysis of covariance $p < 0{\cdot}0004$). It was significantly related to the cumulative dose of doxorubicin ($r = 0{\cdot}488$). Similarly, the change of dimension with rapid diastolic filling (dRF) differed significantly between the groups (table 4) (analysis of variance $p < 0{\cdot}04$, analysis of covariance $p < 0{\cdot}01$) and was inversely related to the cumulative dose of doxorubicin ($r = -0{\cdot}425$). It changed less in patients with a cumulative dose of doxorubicin > 360 mg/m^2 than in patients with a cumulative doxorubicin dose < 180 mg/m^2 ($p < 0{\cdot}003$). The time between minimal cavity dimension and mitral valve opening was slightly longer in patients with a cumulative dose of doxorubicin > 360 mg/m^2 than in patients with a cumulative dose of doxorubicin < 180 mg/m^2, but neither analysis of variance nor analysis of covariance showed significant differences between the groups (table 4). The maximal normalised fibre lengthening rate was similar in all the groups.

Discussion

Little is known about the long term changes of cardiac function after doxorubicin treatment.[26] Because of the long life expectancy after successful antineoplastic treatment in childhood, evaluation of long term doxorubicin cardiotoxicity is important in this age group.[1-4 27]

Endomyocardial biopsy has become the reference standard for monitoring doxorubicin cardiotoxicity; none the less, histological grading has been shown to correlate poorly with left ventricular performance in most studies.[6 7 28] Left ventricular performance seems to be a more important indicator of toxicity than the histological appearance of the right ventricular myocardium. None of the patients we studied had received mediastinal irradiation or had overt cardiomyopathy.

DIASTOLIC FUNCTION AFTER DOXORUBICIN TREATMENT

Most studies of doxorubicin cardiotoxicity have focused on impaired left ventricular ejection. But diastolic function seems to be at least as important.[15-17] We found that diastolic filling was significantly impaired after doxorubicin treatment in childhood. This impairment was related to the cumulative dose of doxorubicin (table 4) and was characterised by an impairment of rapid diastolic filling and an increased change of dimension between minimal cavity dimension and mitral valve opening.

In contrast with the isovolumic relaxation period, that is the interval between aortic valve closure and mitral valve opening, the interval between minimal cavity dimenion and mitral valve opening (tDS-MO) was independent of the timing of aortic valve closure and reflected the timing of mitral valve opening. The change of dimension in this period is usually small.[23 24] An increase in the change of dimension between minimal cavity dimension and mitral valve opening reflects increased changes of left ventricular shape before mitral valve opening—that is incoordinate relaxation and impaired early diastolic function. Similarly, reduced early diastolic filling reflects impaired early diastolic function.

These alterations of diastolic filling could reflect restrictive endomyocardial disease,[29 30] as reported by Mortensen *et al.*[15] Others have reported echocardiographic evidence of altered diastolic properties *during* antineoplastic treatment.[16 17] Our data indicate that impaired early diastolic function can persist at least for some years after the end of treatment.

CONTRACTILE STATE AFTER DOXORUBICIN TREATMENT

Recently, the slope of the end systolic pressure-length relation has been shown to be a load-independent and sensitive index of doxorubicin cardiotox-

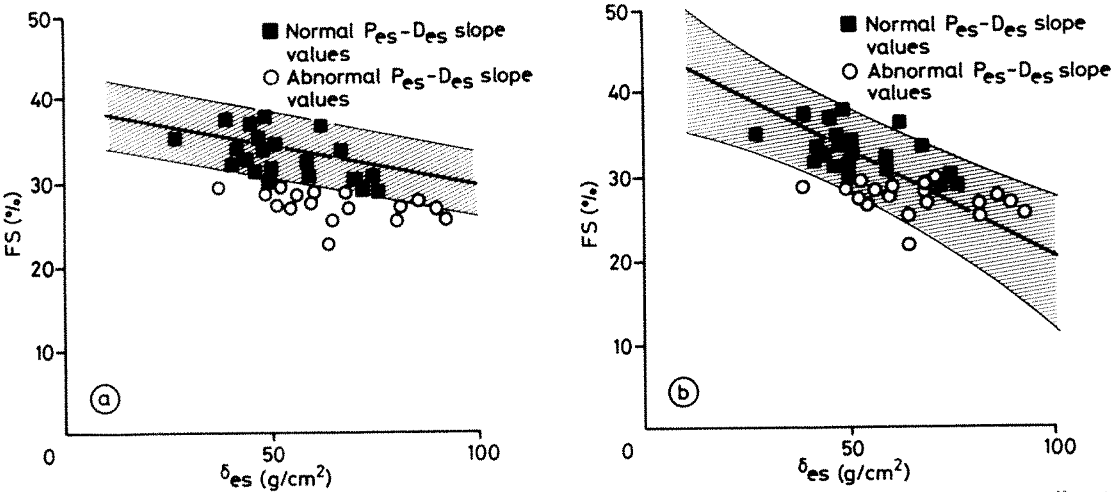

Fig 2 *(a) Individual baseline values for end systolic wall stress and fractional shortening from a study by Borow et al*[10] *and the normal range for the relation between end systolic wall stress* (σ_{es}) *and fractional shortening (FS) as defined by a afterload increase produced by methoxamine in normal subjects.*[10] *The open circles are patients with an abnormal end systolic pressure-length relation* ($P_{es}-D_{es}$). *(b) The same data points together with the normal range as defined by a afterload increase produced by angiotensin II.*[8] *Most of the baseline stress-shortening data outside the normal range as defined by afterload increase with methoxamine are within the normal range as defined by angiotensin II.*

icity.[10] The end systolic stress shortening relations seem to be a more sensitive index than the pressure-length relation.[9 10] The end systolic stress-shortening relations reflect the interaction of forces working on the left ventricle at end ejection and the extent of fibre shortening.[9 10]

We found that doxorubicin treatment in childhood had no effect on end systolic pressure-length and stress-shortening relations 2·1–10·4 years later. Surprisingly the contractile state was slightly increased in patients with a cumulative doxorubicin dose < 180 mg/m². This could be the result of increased sympathetic drive because unlike the normal subjects these patients knew that they were being investigated for possible heart disease.

End systolic wall stress during baseline conditions was significantly increased in patients in whom the cumulative dose of doxorubicin was >360 mg/m². This increase reflects an increased afterload[31] (tables 1 and 2). This result accords with the data reported by Borow *et al*, who showed that the baseline values of end systolic wall stress and fractional shortening predicted the contractile state after doxorubicin treatment[10] (fig 2). But unlike these workers we increased afterload with angiotensin II[8] not methoxamine[10]; this resulted in a different normal range with steeper gradients for the end systolic pressure-length and stress-shortening relations.[8] Angiotensin II has negligible effects on preload, unlike methoxamine, and this difference may have influenced the end systolic pressure-length and stress-shortening relations in these two studies.

Most baseline data for stress-shortening relations that were outside the normal range after the afterload was increased with methoxamine (fig 2a) were within the normal range for studies in which the afterload was increased by angiotensin II in normal subjects (fig 2).[8 10] Although it is normal for systolic emptying to be reduced and end systolic wall stress to be increased when the afterload is increased,[31] a significant increase in end systolic wall stress during baseline conditions is definitely abnormal. So the measurement of the end systolic wall stress during baseline conditions may be an important method of monitoring doxorubicin cardiotoxicity.

Our data show that diastolic function is significantly altered after doxorubicin treatment in childhood. Impaired diastolic function was seen in patients without overt cardiomyopathy and was related to the cumulative dose of doxorubicin. It may be that impairment of left ventricular diastolic function is related to restrictive endomyocardial disease. We did not, however, find that the contractile state was significantly impaired (that is, doxorubicin had no effect on the end systolic pressure-length and stress-shortening relations). None the less, a significant increase of the end systolic wall stress during baseline conditions in patients with high cumulative doxorubicin dose showed that the afterload was increased after doxorubicin treatment in childhood.

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Longitudinal study of ventricular function after the Mustard operation for transposition of the great arteries: a long term follow up

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SUMMARY An earlier study of 25 patients who were investigated by radionuclide angiography after a Mustard procedure showed that they had had evidence of right and left ventricular dysfunction at rest and with exercise. Twenty one (mean age 17·0 years (range 13·7–20·6) 11 female patients) of the original 25 patients were followed up a mean of 4·3 years later (mean 14·6 years (range 12·5–16·0) after the procedure). The group means for resting right and left ventricular ejection fraction and exercise response were not significantly different from those reported five years before. Individual changes in values were within the normal variation seen in serial studies.

This long term longitudinal follow up of patients after the Mustard operation showed that although some patients still had right and left ventricular dysfunction, resting ventricular function and exercise response remained stable over a five year period. This preservation of cardiac function may contribute to the long term survival of patients after the Mustard procedure.

Since 1964 when Mustard first reported his operation to correct transposition of the great arteries,[1] cardiac centres throughout the world have performed this operation. Current mortality is low for uncomplicated cases[2] but there has been concern about postoperative morbidity, including baffle obstruction, residual shunts, pulmonary venous obstructive disease, tricuspid regurgitation, arrhythmias, and right ventricular dysfunction.[3-5]

In 1984 Ramsay *et al* used radionuclide angiographic techniques to study ventricular function in a group who had had a Mustard procedure at the Royal Childrens' Hospital, Melbourne.[6] We report a longitudinal follow up and update on this group of patients who we studied a mean of 4·3 years after the initial study and 14·6 years after their original operation.

Patients and methods

PATIENTS

In the earlier study 25 patients with Mustard's operation for D-transposition of the great arteries were investigated between August 1982 and March 1983. The clinical features of this group of patients were described in the earlier paper.[6]

Since the first study four patients (cases 1, 15, 18, and 23 in table 2 of Ramsay *et al*'s paper[6]) had implantation of pacemakers for management of sinus node dysfunction and one of these (case 18) died of right ventricular failure in 1985. Another (case 12) underwent an operation for obstruction of the superior vena cava after the completion of the first study and subsequently died of right ventricular failure before the start of the second study.

We reviewed the data on the two patients who had died in the interval between the two studies. The first (case 18) had an abnormal resting right ventricular ejection fraction by the equilibrium method but a normal first pass result. He also had no increase of ejection fraction at exercise by either method. The second (case 12) had abnormal right ventricular ejection fraction at rest with no increase at exercise by either method.

One patient (case 20) was lost to follow up, and another (case 22) refused consent for the study. We studied the remaining 21 patients between May 1986 and May 1987.

All the patients claimed to be symptom free and to

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be leading normal lives with unrestricted physical activity at the time of the study. Their mean age was 17·0 years (range 13·7–20·6) at the time of the second study which was performed a mean of 14·6 years (range 12·5 to 16·0) after operation. There were 10 male patients and 11 female patients and there were no significant sex differences in age or the interval since operation.

Methods

Twenty patients had electrocardiograms recorded and 19 had chest *x* rays, 24 hour Holter monitor, and treadmill exercise tests according to the modified Bruce protocol.[7] All 21 patients had a radionuclide study to measure right and left ventricular ejection fraction at rest and exercise (supine bicycle ergometer) by both the equilibrium and gated first pass techiques in the Department of Nuclear Medicine, Alfred Hospital, Melbourne, where the original tests were done. Details of these techniques were fully discussed in the earlier paper by Ramsay *et al.*[6] Imaging angles were adjusted for the rotation of the heart. In accordance with standard laboratory practice,[8] the exercise workload was increased every three minutes instead of every four minutes as in the previous study. Apart from this, the equipment, technical aspects, and protocol were identical to the 1982 study.

The criteria for normal ejection fraction and exercise response were those used for the first study.[6 9] Normal right ventricular ejection fraction was defined as ⩾45% and left ventricular ejection fraction as ⩾55%. Normal exercise ejection fraction response was defined as an increase of >5% from rest to maximal exercise or a value of >75% at both rest and exercise. Others have reported similar values in children.[9]

For comparison with the previous study we excluded data on the four patients in whom the studies were not repeated.

STATISTICAL ANALYSIS

Values in the paper are mean (1 SD). We used the unpaired *t* test to assess the significance of the sex differences for the workload and ventricular function. A paired *t* test was used to compare the mean ventricular ejection fractions of the two studies. We used the coefficient of variation (defined as the standard deviation of (1982 ejection fraction minus 1987 ejection fraction) divided by the mean of 1982 ejection fraction) to assess the variability of the serial ejection fraction results.

Results

The mean cardiothoracic ratio for the 19 chest *x* rays was 0·53 (0·05).

The electrocardiograms showed that 12 of 20 patients had sinus rhythm, with five patients having a low atrial or junctional rhythm. Three had implanted pacemakers. Twenty four hour Holter monitor studies showed that five of 19 patients had normal sinus rhythm. In the others sinus rhythm alternated with low atrial and junctional rhythm (10 cases), atrioventricular dissociation (five cases), and/or frequent ventricular extrasystoles (two cases).

In the exercise treadmill test seven of 19 patients had exercise tolerance less than the 10th percentile for age and sex, seven patients were between the 10th and 25th percentile, and one was between the 25th to 50th percentile. Only four patients (cases 2, 4, 11, and 25) had exercise tolerance above the 75th percentile. Three patients (13, 19, and 23) had frequent ventricular extrasystoles and two (cases 13 and 21) had ST depression of 1 mm during exercise which quickly became normal in the recovery phase.

RESULTS OF SUPINE EXERCISE ON A BICYCLE ERGOMETER

The mean heart rate at rest was 66 (9) beats/min and at maximal exercise it was 130 (21) beats/min (an increase of 97%). The mean systolic blood pressure at rest was 119 (6) mm Hg and at maximal exercise it was 154 (17) mm Hg (an increase of 29%).

The mean maximal workload achieved at peak exercise was 1·68 (0·34) W/kg. There was a significant difference ($p \leq 0.001$) between the mean maximal workload of the male patients (1·93 (0·21) W/kg) and of the female patients (1·45 (0·28) W/kg). In the earlier study the mean maximal workload was 1·45 (0·4) W/kg. At that time there was no significant difference between the workload attained by the male patients (1·58 (0·49) W/kg) and that obtained by the female patients (1·32 (0·29) W/kg). Although the workload performance per kilogram body weight by the male patients improved significantly over the five year period ($p < 0.01$), that of the female patients did not change significantly.

RADIONUCLIDE DATA

Table 1 shows the individual ejection fraction results. Figures 1–4 show the relation between the results obtained at this study and the results obtained in the earlier one.

Two out of 21 results for right ventricular ejection fraction measured by the equilibrium method could not be analysed. All right ventricular ejection fractions measured by first pass and all left ventricular ejection fractions by the equilibrium method were suitable for analysis. One left ventricular ejection fraction by first pass was not available for analysis because of bolus breakup. All 21 patients had their right and left ventricular ejection fractions measured

Table 1 *Right and left ventricular ejection fractions in 1987 (the results obtained in 1982 are given in parentheses)*

	Right ventricular ejection fraction (%)				*Left ventricular ejection fraction (%)*				
	Equilibrium study		*First pass study*		*Equilibrium study*		*First pass study*		
Case No	*Rest*	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*	*Workload (W/kg)*†
1	28 (44)	38 (57)	42 (56)	44 (62)	44 (49)	40 (52)	64 (65)	59 (62)	2 0 (1·7)
2	47 (67)	49 (59)	69 (*)	69 (*)	71 (*)	78 (*)	68 (*)	75 (*)	1 8 (1·6)
3	* (*)	* (*)	57 (57)	64 (58)	64 (*)	78 (*)	61 (57)	76 (67)	1·4 (1·2)
4	59 (32)	48 (48)	59 (46)	69 (61)	72 (51)	75 (66)	66 (53)	83 (69)	1 6 (1·8)
5	42 (60)	48 (59)	48 (55)	48 (57)	67 (54)	63 (53)	59 (52)	69 (57)	1 9 (0·9)
6	57 (49)	65 (55)	72 (72)	78 (65)	57 (65)	66 (55)	58 (66)	56 (66)	2·1 (2·1)
7	46 (50)	55 (39)	48 (59)	68 (48)	69 (66)	75 (71)	67 (63)	66 (75)	1 5 (1 4)
8	50 (33)	51 (40)	50 (55)	61 (70)	51 (72)	82 (76)	60 (78)	71 (89)	1·9 (0·8)
9	60 (57)	62 (58)	69 (80)	73 (76)	64 (76)	63 (81)	83 (78)	88 (91)	1 9 (1 8)
10	59 (52)	54 (59)	51 (57)	56 (42)	89 (95)	92 (86)	93 (76)	92 (79)	1 9 (1 7)
11	48 (42)	48 (48)	65 (46)	63 (60)	75 (55)	77 (66)	74 (56)	91 (79)	1·9 (2·2)
12	— (38)	— (39)	— (44)	— (42)	— (57)	— (72)	— (62)	— (82)	— (1 3)
13	48 (57)	47 (52)	44 (47)	45 (65)	49 (53)	51 (61)	51 (50)	65 (61)	1 9 (1·0)
14	49 (46)	46 (40)	62 (38)	53 (51)	60 (47)	55 (51)	* (45)	* (48)	2 1 (2·1)
15	40 (43)	25 (35)	40 (50)	49 (48)	55 (58)	73 (75)	78 (*)	80 (*)	1·3 (1 0)
16	53 (54)	54 (48)	58 (56)	57 (63)	70 (51)	81 (66)	55 (75)	77 (73)	1 6 (1·1)
17	* (40)	* (36)	58 (55)	60 (64)	62 (54)	68 (52)	59 (61)	63 (64)	1·6 (1 4)
18	— (44)	— (41)	— (54)	— (54)	— (76)	— (76)	— (65)	— (69)	— (2·0)
19	55 (48)	53 (39)	54 (60)	61 (54)	66 (58)	76 (68)	73 (53)	88 (73)	1 3 (1·3)
20	— (44)	— (56)	— (*)	— (*)	— (48)	— (49)	— (*)	— (*)	— (1 7)
21	42 (51)	48 (49)	60 (59)	65 (60)	54 (73)	70 (70)	79 (65)	79 (78)	2 2 (1·3)
22	— (48)	— (37)	— (52)	— (49)	— (63)	— (54)	— (72)	— (69)	— (1 0)
23	45 (61)	44 (61)	51 (49)	50 (53)	64 (71)	61 (79)	62 (62)	61 (65)	1 1 (1 2)
24	62 (56)	58 (41)	62 (70)	60 (63)	60 (84)	68 (76)	69 (72)	80 (77)	1 1 (1 2)
25	56 (60)	65 (54)	60 (62)	55 (60)	80 (59)	90 (81)	66 (68)	75 (80)	1·6 (1 8)

*Technically unsatisfactory result; †peak workload/weight; — patients not restudied in 1987

at rest and with exercise by either the first pass or equilibrium technique. The use of both equilibrium and first pass technique gave a better yield of results than use of either test alone. The difference in the values obtained by the two methods was discussed in the previous paper.[6]

There was no statistical difference in resting and exercise right and left ventricular ejection fraction results by either method between the male and female patients.

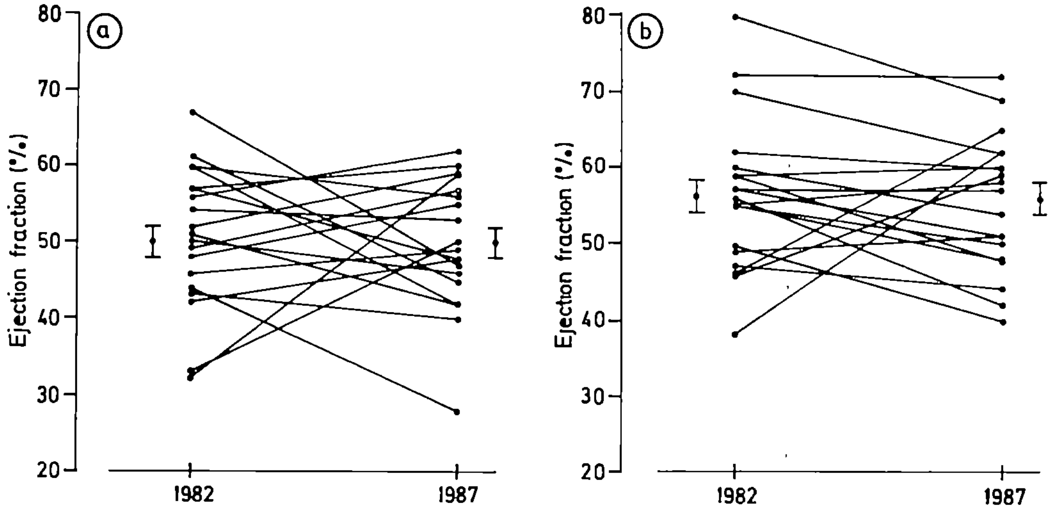

Fig 1 *Individual right ventricular ejection fractions at rest and means (SEM) for 1982 and 1987 measured by (a) the equilibrium method and (b) the first pass method.*

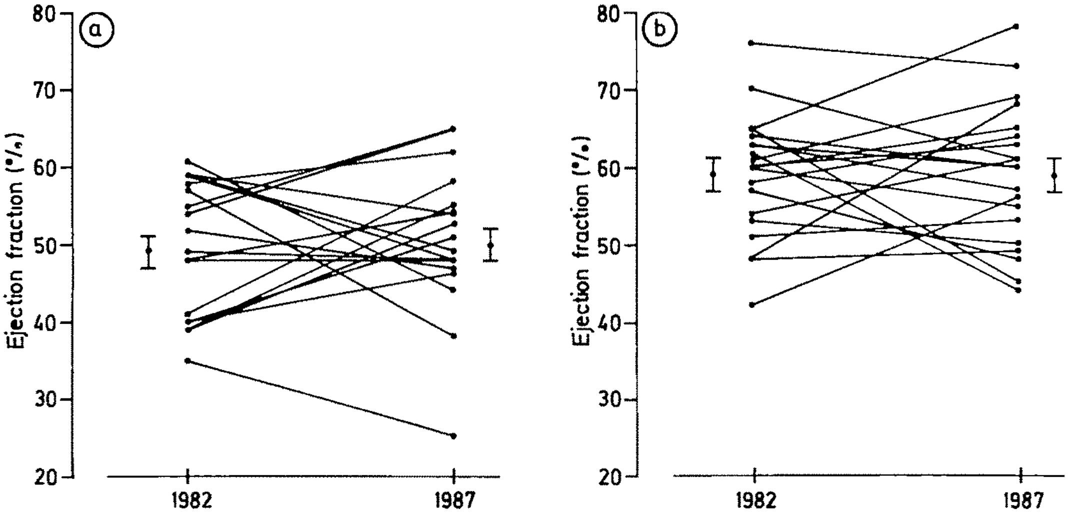

Fig 2 *Right ventricular ejection fractions at maximal exercise and means (SEM) for 1982 and 1987 measured by (a) the equilibrium method and (b) the first pass method.*

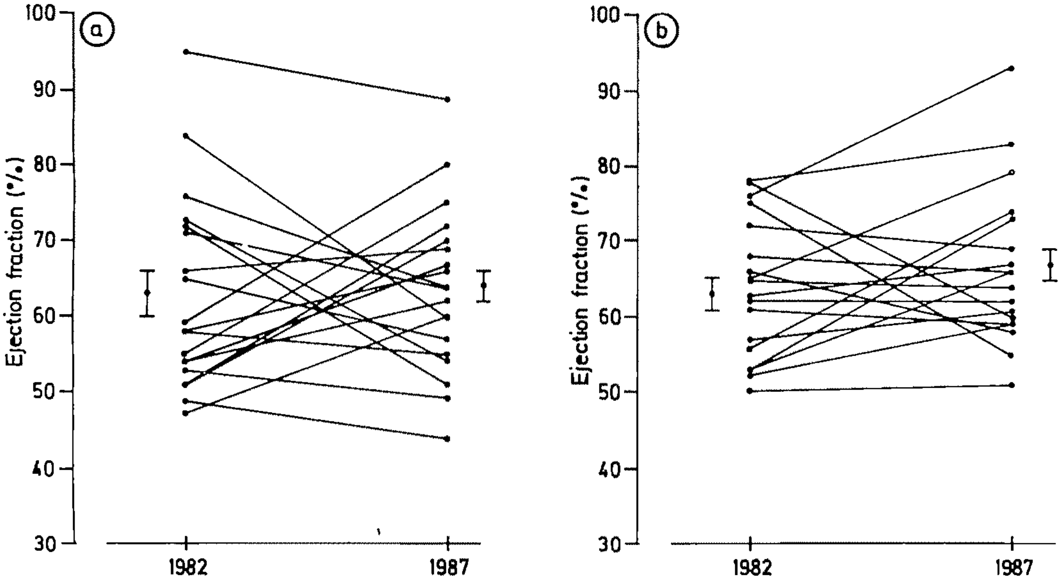

Fig 3 *Left ventricular ejection fractions at rest and means (SEM) for 1982 and 1987 measured by (a) the equlibrium method and (b) the first pass method.*

Right ventricular ejection fraction
The mean resting right ventricular ejection fractions by equilibrium and first pass were 50 (8)% and 56 (9)% respectively and the mean exercise right ventricular ejection fractions by equilibrium and first pass were 50 (9)% and 59 (9)% respectively (table 2). The resting right ventricular ejection fraction was normal in 79% (15/19) of the patients by the equilibrium technique and in 86% (18/21) of patients by the first pass technique. The exercise response,

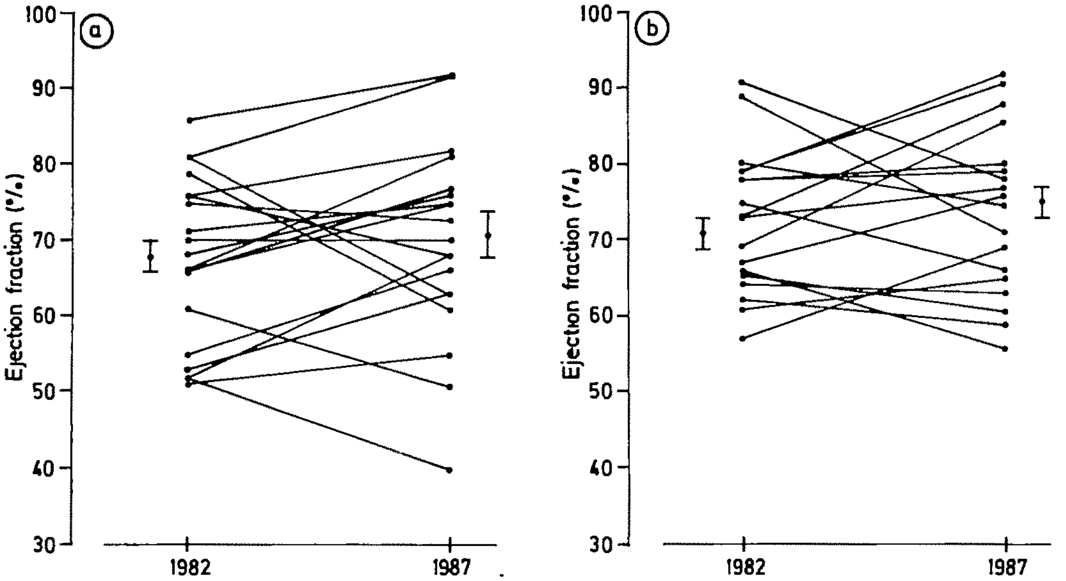

Fig 4 *Left ventricular ejection fractions at maximal exercise and means (SEM) for 1982 and 1987 measured by (a) the equilibrium method and (b) the first pass method.*

however, was normal in only 32% (6/19) of the patients by the equilibrium technique and 33% (7/21) of the patients by the first pass technique.

Left ventricular ejection fraction

The mean resting left ventricular ejection fractions by equilibrium and first pass were 64 (11)% and 67 (10)% respectively and the mean exercise ejection fractions by the equilibrium and first pass techniques were 71 (12)% and 75 (11)% respectively. The resting left ventricular ejection fraction was normal in 81% (17/21) of patients by the equilibrium method and in 95% (19/20) of the patients by the first pass method. The left ventricular exercise response was normal in 67% (14/21) of the patients by the equilibrium techique and 75% (15/20) of the patients by the first pass technique.

Serial ejection fraction measurements

Table 2 shows the mean left and right ventricular ejection fractions of the two studies. Paired *t* testing showed no significant change in the right or left ventricular ejection fraction at rest or execise by either method over the 4·3 year period (figs 1–4). Paired *t* testing showed no significant change over 4·3 years in the response of the right or left ventricles to exercise (table 2).

Figures 1–4 show the variation in ejection fraction values between the initial and the follow up studies for all patients. To assess the possible significance of the individual change in ejection fraction over this 4·3 year period we calculated the coefficients of variation between initial and follow up values for the ejection fraction (table 3). These values were similar for the right and left ventricles, both at rest and during exercise.

Table 2 *Mean (SD) ejection fraction values (%)*

	Right ventricle		*Left ventricle*	
	Equilibrium	*First pass*	*Equilibrium*	*First pass*
Resting:				
1987 study	50 (8)	56 (9)	64 (11)	67 (10)
1982 study	50 (9)	56 (10)	63 (13)	63 (10)
Exercise:				
1987 study	50 (9)	59 (9)	71 (12)	75 (11)
1982 study	49 (9)	59 (8)	68 (11)	71 (11)

Table 3 *Coefficients of variation for changes (%) in ejection fraction seen in individual patients between 1982 and 1987*

	Right ventricle		*Left ventricle*	
	Equilibrium	*First pass*	*Equilibrium*	*First pass*
Resting	23	18	24	18
Exercise	15	13	23	17

Discussion

We report a 4·3 year longitudinal follow up study of ventricular function at rest and exercise in a group of patients who had undergone the Mustard procedure a mean of 14·6 years earlier, and whose ventricular function had been previously studied by Ramsay *et al.*[6] Twenty one of the original 25 patients investigated by Ramsay *et al* were re-evaluated in the present study.

The electrocardiograms and 24 hour Holter monitor tapes showed evidence of sinus node dysfunction in most patients. Significant dysfunction requiring pacemaker implantation was seen in four patients. An increasing frequency of arrhythmias with time has been reported in patients with intra-atrial repair for transposition of the great arteries in other follow up series.[10 11]

The exercise tolerance of this group of patients on the treadmill was lower than in the normal population[7] and was skewed towards the lower percentiles. This is consistent with the report by Mathews *et al* who found that despite their apparently normal clinical state, patients have subnormal exercise variables after the Mustard procedure.[12] In the present study during the supine bicycle exercise test the male patients attained significantly higher workloads than the female patients, although five years before there were no differences between the sexes. Over the same five year period the male patients also had significant improvement of their workload performance compared with the first study while the female patients showed no change in their workload performance. It seems that the increased muscularity of the male patients during the adolescent growth period has led to their better workload performance. But the higher workload achieved by the boys had no bearing on ventricular ejection fraction—there was no significant difference in ventricular function between the sexes. Parrish *et al* found similar sex and age differences when they investigated ventricular function during exercise in normal children by a radionuclide technique.[9]

As well as arrhythmias, another major concern in late follow up of patients after a Mustard procedure is how well the right ventricle can adapt to an increased afterload in its role as a systemic ventricle and whether its function will deteriorate with time. Cineangiography and radionuclide angiography of patients after the Mustard procedure showed evidence of right ventricular dysfunction.[13-15]

In this study the mean resting and exercise right ventricular function of the group remained unchanged over the period of 4·3 years. To assess the significance of individual changes in ventricular ejection fraction, we calculated the values of the coefficients of variation for individual changes in right ventricular rest and exercise ejection fraction between the present and previous study (table 3). We compared them with the values obtained from an earlier study done in this laboratory[16] in which serial left ventricular ejection fraction measurements were examined over a period of several months. There are no other comparative studies of a group of patients studied by radionuclide angiography over a period of years. The coefficients of variation of the earlier study ranged from 16% to 26%[16] and were thus comparable with those of the present study (table 3). Therefore, at this time, the differences in individual values could be accounted for by normal variation between serial studies.

The finding that overall right ventricular function at rest and at exercise was maintained and did not deteriorate during this interval is important. It suggests that any perioperative insult that damaged the myocardium was not progressive in this group of survivors for this period of follow up, and also that the right ventricle was able to cope as a systemic ventricle and provide a reasonable function over this period.

No other longitudinal study of similar patients is available for comparison. The results of Hurwitz *et al*,[17] however, accord with our findings. They measured the resting right ventricular ejection fraction by radionuclide techniques in three different sets of patients undergoing the Mustard procedure. One group was measured before the Mustard operation, one group 6–12 months after the Mustard procedure, and the last group three years after the Mustard procedure. They found no statistical difference in the mean resting right ventricular ejection fractions between the three groups, and these results also resembled those of their normal population. They proposed that the group right ventricular function did not deteriorate in a three year period after the Mustard procedure. Their conclusions could only be tentative because their study was not a longitudinal one and the length of follow up was relatively short.

Another group used as a model for comparison with patients after a Mustard procedure are patients with congenitally corrected transposition—that is where the morphologically right ventricle functions as the systemic ventricle. Parrish *et al* used radionuclide angiography in patients after a Mustard procedure and in congenitally corrected transposition and found no increase in right ventricular ejection fraction with exercise in either group.[18] But the group they studied had associated cardiac abnormalities. Benson *et al* studied eight patients with congenitally corrected transposition without haemodynamically significant associated defects and reported that the mean systemic right ventricular ejection fraction was 48 (4)% at rest and 64 (4)% with exercise—that is a normal exercise response.[19] Whether this is an appropriate model is debatable. None the less, the right ventricle was coping well as the systemic ventricle at the time of study in these patients with congenitally corrected transposition.

The present study also shows that left ventricular resting function and exercise response were also stable over the 4·3 years. Hence both the left and the right ventricles—that is the heart as a whole—did not show any change in functional state. This suggests that there was no progressive global damage to the myocardium.

Whereas most patients had normal resting right and left ventricular ejection fractions, in two thirds the response of the right ventricle to exercise was abnormal and in about one quarter the response of the left ventricle remained abnormal. The long term prognostic implications of these findings are unclear. A study by Bonow *et al* that examined left ventricular ejection fraction in adult patients with aortic incompetence suggested that an abnormal response to exercise may be predictive of progressive ventricular dysfunction.[20] Bonow *et al* also found that patients who were apparently symptom free could have an abnormal cardiac reserve.[20] Thus the apparent lack of correlation between clinical symptoms and abnormalities of ventricular contraction is not unique to patients with a Mustard repair. It is found in other patients with congenital heart disease. Del Torso *et al* showed a similar trend in children after a Fontan procedure.[21] Further long term follow up studies are needed to assess the interrelations between abnormal exercise response, clinical symptoms, and prognosis after the Mustard procedure.

In conclusion, this longitudinal study on a group of patients after the Mustard procedure showed that right and left ventricular function at rest and exercise remained stable over a 4·3 year period that started at least eight years after the original operation. Evidence of ventricular dysfunction remained unchanged. The lack of progresson of myocardial dysfunction may contribute to the long term survival[22] and future outcome of patients after the Mustard procedure. However, this remains to be confirmed by further studies.

We thank Dr Rodney Hicks for performing some of the rest and exercise radionuclide ventriculographic studies.

Addendum

Since this paper was accepted for publication one patient has developed severe congestive heart failure. At follow up this patient (case 1 in table 1), showed the largest fall in both first pass and equilibrium right ventricular ejection fraction values and the lowest equilibrium left ventricular ejection fraction results of any patient in this study. In infancy he had two direct operations for severe left ventricular outflow obstruction as well as secondary revision of the original Mustard operation, and in 1985 he required an implantation of a pacemaker because of atrioventricular dissociation. He has been accepted for cardiac transplantation.

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Left ventricular function in double inlet left ventricle before the Fontan operation: comparison with tricuspid atresia

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SUMMARY Fourteen patients with double inlet left ventricle and nine patients with tricuspid atresia had biplane left ventricular angiography with simultaneous measurement of left ventricular pressure by micromanometer. Age distribution, haemodynamic function, and previous palliative operation were similar in the two groups. Left ventricular volumes were calculated frame by frame throughout the cardiac cycle by Simpson's rule. The end diastolic volume index was similar in the two groups, but the ejection fraction was significantly lower in tricuspid atresia. Left ventricular peak filling and emptying rates were also lower in tricuspid atresia, although heart rates in the two groups were similar. End diastolic shape index was significantly higher in patients with tricuspid atresia, indicating a more globular shape, and changed less during systole, suggesting differences in the mechanism of ejection between the two groups. Analysis of pressure-volume loops showed normal phase relations between pressure and volume, but systolic stroke work was reduced in tricuspid atresia and correlated with stroke volume and shape change.

Left ventricular function was impaired in patients with tricuspid atresia when compared with those with double inlet left ventricle and this finding may reflect structural differences caused by the absence of one atrioventricular connection.

Various radical palliative procedures based on Fontan's original operation have been introduced to correct the circulation in patients with tricuspid atresia or double inlet left ventricle.[1 2] It has been suggested that "normal" left ventricular function is of fundamental importance to survival after these procedures.[3] More recently, however, several groups have shown depressed left ventricular ejection fraction in patients with tricuspid atresia both before and after primary palliative procedures such as systemic to pulmonary shunting and pulmonary artery banding.[4-6] There is little published data on ventricular function in double inlet left ventricle but our own preliminary data have suggested that some indices of left ventricular function are normal or near normal in these patients.[7] It is somewhat surprising, therefore, if ventricular function is an important determinant of outcome, that perioperative mortality is lower in patients with tricuspid atresia than in patients with double inlet left ventricle undergoing modified Fontan procedures.[8]

We studied left ventricular function in a group of patients with double inlet left ventricle and compared these results with similar measurements in patients with tricuspid atresia in order to explore the possible causes of any differences between the two groups and to assess the influence of ventricular function on the outcome of corrective surgery.

Patients and methods

TERMINOLOGY

The segmental approach to the classification of univentricular hearts has been described in detail elsewhere.[9] In hearts with a univentricular connection the atrial chambers connect either entirely or predominantly to one ventricle. In all patients in this study the atria connected to a main chamber of left ventricular morphology and the right ventricle was rudimentary.

Patients were described as having double inlet left

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ventricle when one atrioventricular valve and more than 50% of the other valve were connected to a morphologically left ventricle. Under these circumstances one or other of the atrioventricular valves may be stenotic, imperforate, straddling, or overriding; these additional abnormalities are described separately (table 1). When there was a common atrioventricular valve the connection was said to be double inlet when > 75% of the valve was connected to the left ventricle.

The other group had classic tricuspid atresia, that is absence of the right atrioventricular connection with interposition of sulcus tissue between right atrium and the rudimentary right ventricle. No patient had the much rarer abnormality of atrioventricular concordance with imperforate right atrioventricular valve. The distinction between these two abnormalities was made by cross sectional echocardiography according to previously described echocardiographic criteria.[10]

The position of the rudimentary right ventricle and the ventriculoarterial connection in each patient was determined by cross sectional echocardiography and angiography.

PATIENTS

Fourteen patients (mean age 73, range 4–216 months) with an echocardiographic diagnosis of double inlet left ventricle and nine patients (mean age 55, range 6–144 months) with tricuspid atresia underwent cardiac catheterisation. All patients were being assessed for suitability for the Fontan operation. Ten patients with double inlet left ventricle and six patients with tricuspid atresia were studied a mean (SD) of 32 (17) months after palliative procedures. Table 1 shows the full sequential diagnosis and details of previous operation for each patient.

Cardiac catheterisation

Cardiac catheterisation was performed during general anaesthesia. Table 2 summarises the haemodynamic data recorded before angiography. There were no significant differences between the groups for left ventricular peak systolic pressure, end diastolic pressure, or aortic oxygen saturations. Orthogonal biplane left ventricular cineangiograms were recorded on 35 mm cinefilm at a frame rate of 50 or 75 frames per second depending on the heart rate. A

Table 1 *Sequential diagnosis and previous operation in 14 patients with double inlet left ventricle and nine with tricuspid atresia*

Patient	*AV connection**	*RV to LV relation*	*VA connection*	*Associated lesions*	*Operation*
			Double inlet left ventricle		
1	2 valves	Right	Concordant	Absent left PA	Waterston shunt
2	2 valves	Left	Single outlet	Pulmonary atresia	Waterston and Blalock shunt
3	Imperforate right AVV	Right	Concordant	—	—
4	2 valves	Right	Discordant	Subpulmonary stenosis and valvar PS	—
5	2 valves	Left	Discordant	Valvar PS	Blalock shunt
6	2 valves	Right	Discordant	Ao interruption	Repaired Ao interruption, PA band
7	2 valves	Left	Discordant	—	PA band
8	Common	Right	Disconcordant	Ao coarctation	Repaired coarctation, PA band (tight + +)
9	2 valves	Right	Concordant	Pulmonary vascular disease	—
10	2 valves	Right	Discordant	Ao coarctation	Repaired coarctation
11	2 valves	Left	Discordant	—	PA band
12	2 valves	Right	Discordant	Ao interruption, restrictive VSD	Repaired Ao interruption, enlarged VSD, PA band
13	2 valves	Right	Discordant	—	PA band
14	2 valves	Left	Double outlet LV	PS	Shunt
			Tricuspid atresia		
15	Tricuspid atresia		Discordant	Restrictive VSD	PA band
16	Tricuspid atresia		Double outlet RV	Subpulmonary stenosis, pulmonary valve stenosis	Shunt
17	Tricuspid atresia		Concordant	Subpulmonary stenosis	Shunt × 2
18	Tricuspid atresia		Concordant	Subpulmonary stenosis	Shunt
19	Tricuspid atresia		Double outlet RV	—	Band
20	Tricuspid atresia		Discordant	—	Band
21	Tricuspid atresia		Discordant	—	PA band
22	Tricuspid atresia		Concordant	—	Shunt
23	Tricuspid atresia		Single outlet	Pulmonary atresia	Shunt × 2

*All patients have situs solitus.

PA, pulmonary artery; Ao, aortic; PS, pulmonary stenosis, VSD, ventricular septal defect; AVV, atrioventricular valve; RV, right ventricle; LV, left ventricle.

Table 2 *Haemodynamic data (mean (SD)) recorded before angiography*

	Tricuspid atresia	*Double inlet left ventricle*	*p*
Peak LV systolic pressure (mm Hg)	100 (24)	108 (21)	NS
LV end diastolic pressure (mm Hg)	9 (4)	8 (4)	NS
Aortic oxygen saturation (%)	86 (3)	84 (8)	NS

LV, left ventricular

mark, coinciding with the R wave of the patient's electrocardiogram, was recorded on the cinefilm. After the position of the rudimentary ventricle had been displayed by echocardiography, the angiographic projections were selected to show the interventricular septum. The projections selected were direct anteroposterior and lateral when the rudimentary chamber was to the left of the main chamber and 30° right anterior oblique-60° left anterior oblique when it was to the right. In 12 of the patients with double inlet left ventricle and in five with tricuspid atresia left ventricular pressure was measured with a micromanometer tipped catheter (Millar Instruments) during ventriculography. The output of this catheter was recorded at a paper speed of 200 mm/s along with an electrocardiogram and an event mark that coincided with the appearance of contrast medium in the ventricle. Thus it was possible to synchronise the angiogram and pressure recordings. At the end of the study the patient was moved 10 cm with a catheter in the left ventricle for later calibration of the cinefilm.

ANALYSIS OF ANGIOGRAMS

Only normally conducted beats were analysed. Extrasystoles and post-extrasystoles were excluded. Our method of analysis has been described in detail previously.[11] Briefly, successive cineframes were projected on to a Summagraphics digitising plate interfaced with a Prime 750 computer. The left ventricular outline, excluding the rudimentary right ventricle, was traced frame by frame, starting and finishing with frames corresponding to the R wave of the electrocardiogram. Approximately 100 x,y coordinates were recorded for each outline and stored on magnetic tape for later analysis. This procedure was repeated for the same cycle in the other angiographic view and finally the corresponding left ventricular pressure trace was digitised on the same equipment.

From this stored data the following were derived:

Left ventricular volume

Because the shape and position of these ventricles are abnormal it is inappropriate to measure their volume from single plane angiograms according to the geometric assumptions derived from the normal left ventricle. In this study we calculated ventricular volume from the orthogonal biplane angiograms using Simpson's rule. This is a multiple slice method which overcomes some of the geometric assumptions inherent in other methods of calculating left ventricular volume. Although no angiographic method is perfect, our method, previously described in detail, was accurate when compared with left ventricular cast volumes measured by fluid displacement.[12] Briefly, the left ventricle was divided into 40 equal slices along its long axis. The cross sectional area of each segment was assumed to be an ellipse and its major and minor dimensions were calculated from each of the angiographic views. The volume of the ventricle was derived from the sum of the volume of each slice by applying Simpson's rule (fig 1).

Ventricular volume was measured frame by frame throughout the cardiac cycle and displayed along with its first derivative, dVol/dT (fig 2). End diastolic and end systolic volumes were later corrected for body surface area and expressed in ml/m^2. The ejection fraction was calculated in the usual way. Peak rates of ventricular filling and emptying were taken as the maximum positive and negative deflections on the first derivative of the volume-time curve and were normalised by dividing by end diastolic volume (units = s^{-1}).

Ventricular shape index

This is a measure of the roundness of the outline of the ventricular cavity (fig 2) that is independent of volume. Calculated as 4π (cavity area)/(perimeter)^2 × 100 it has a maximum value of 100 when the cavity outline is circular and 0 when the cavity is obliterated. The normal left ventricle shows a progressive reduction in shape index throughout systole, as it becomes a less circular shape.[11] In this study end diastolic, end systolic, and percentage systolic change were taken as an average of the two angiographic views.

Pressure-volume relations

The frame by frame measurement of ventricular volume has been described above. The derived volume-time curve and the simultaneous digitised pressure trace were combined to give an instantaneous pressure-volume loop. The left ventricular systolic stroke work performed on the circulation is equal to the area enclosed by the loop[13] and this was measured by automatic planimetry and expressed in J/beat/m^2 body surface area (1 J = $1{\cdot}36 \times 10^{-4}$ mm Hg.ml). The cycle efficiency of the loops was expressed as a ratio of the area of the loop to that of a square or rectangle that just encloses it[14] (that is the ratio of actual work done to the maximum possible for a

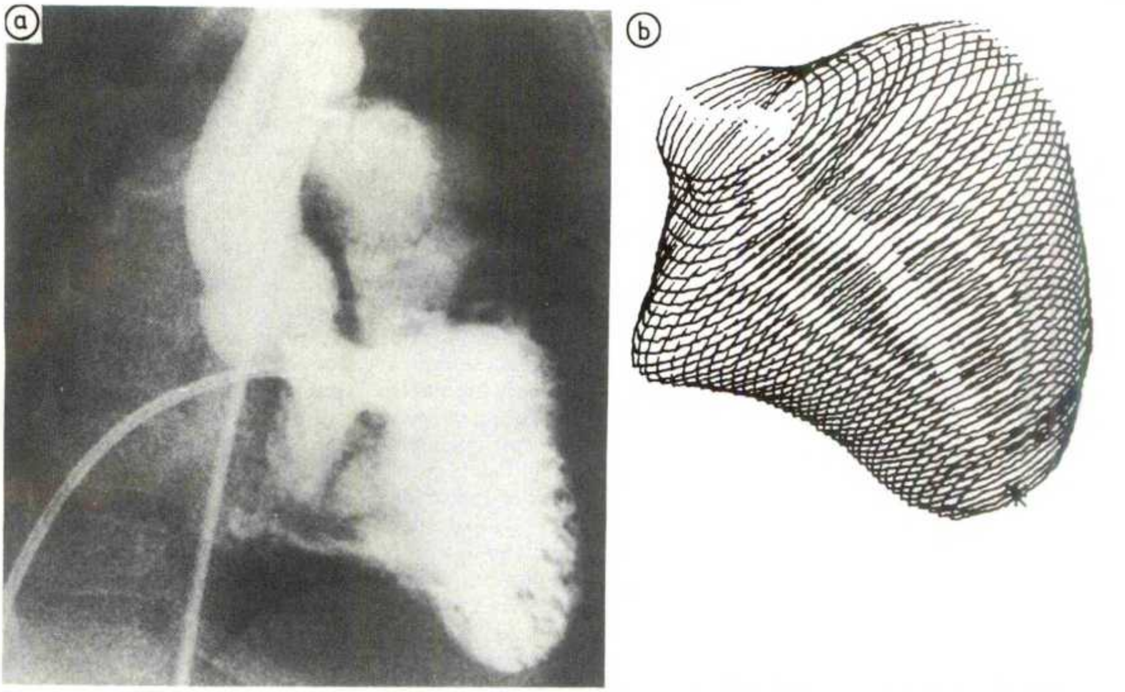

Fig 1 *Left ventricular angiogram for patient 1 (a) with computer derived three-dimensional construction (b) from which volume calculations were made. Accurate reproduction of the ventricular shape and contour is possible.*

ventricle with the same stroke volume and pressure change).

STATISTICAL ANALYSIS

Group data were compared by standard *t* tests and the null hypothesis was rejected when $p < 0{\cdot}05$. We used linear regression analysis by the method of least squares to examine correlations between variables.

Results

No patient had important atrioventricular valve regurgitation. Table 3 summarises the data derived from the angiograms. Mean (SD) end diastolic volume was 136 (32) and 129 (40) ml/m^2 for the groups with double inlet left ventricle and tricuspid atresia respectively ($p = NS$). End systolic volume, however, was significantly lower in patients with double inlet left ventricle (45 (18) *v* 64 (26) ml/m^2 ($p = \; < 0{\cdot}05$)). Thus ejection fraction was higher in the double inlet group (74 (9) *v* 51 (6·5)%, $p < 0{\cdot}001$). Furthermore, nine patients in the double inlet group had an ejection fraction of $\geqslant 75\%$ and only one patient had an ejection fraction of $< 60\%$. In contrast none of the patients with tricuspid atresia had an ejection fraction of $> 60\%$ (fig 3). There were no differences in ventricular volumes or ejection fraction when patients in the various operative subgroups were compared and there was no significant relation between ejection fraction and age, age at or time from operation, or aortic oxygen saturation for either group.

The ventricular shape index at end diastole (averaged from the two angiographic views) was higher in tricuspid atresia (88) (6) *v* 81 (6) $p < 0{\cdot}05$), indicating a more globular shape. Systolic shape index change in patients with tricuspid atresia was reduced (5·8 (4·3) *v* 18 (7)%, $p < 0{\cdot}001$), suggesting differences in the mechanism of ejection between the two groups. There was a significant correlation between systolic shape index change and ejection fraction (all patients, $r = 0{\cdot}63$, $p < 0{\cdot}02$).

Peak rates of ventricular filling corrected for end diastolic volume were 5·9 (2·5) and 4·1 (1·2) s^{-1} for the groups with double inlet or tricuspid atresia respectively ($p < 0{\cdot}05$). There was a strong negative correlation between peak filling rate and RR interval in the patients with double inlet left ventricle ($r = -0{\cdot}72$, $p < 0{\cdot}001$) but not in those with tricuspid atresia ($r = -0{\cdot}47$, $p = NS$). Time to peak filling rate was less in tricuspid atresia (66 (22) *v* 82 (40) ms) but this difference did not reach statistical significance. The peak rate of ventricular emptying was also reduced in patients with tricuspid atresia

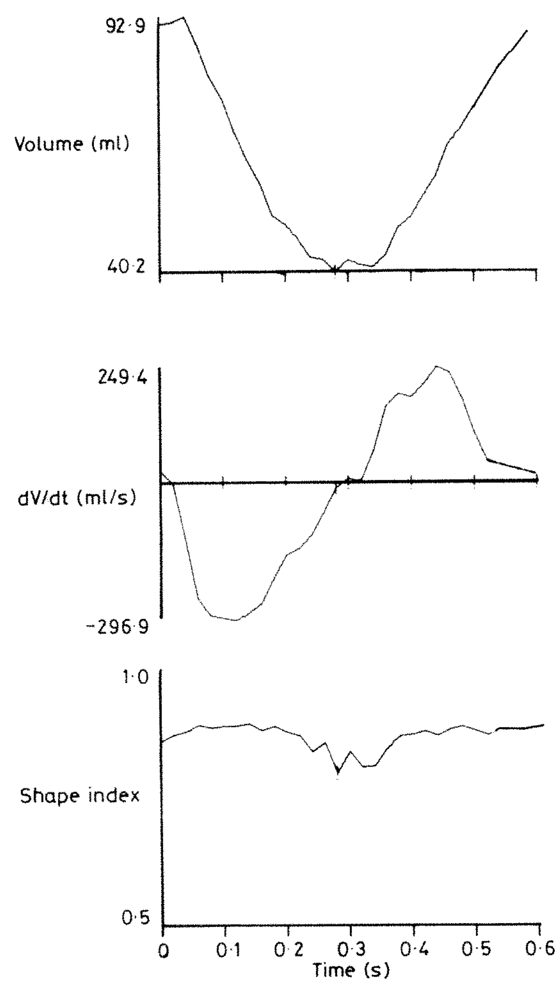

Fig 2 *Typical plots showing left ventricular volume, rate of change of volume, and shape index throughout the cardiac cycle.*

(3·4 (1·2) *v* 5·2 (2·6), $p < 0\cdot05$) but there was no difference in time to peak ejection rate between the two groups.

PRESSURE-VOLUME RELATIONS

Pressure-volume loops were constructed in five of the patients with tricuspid atresia and in 12 with double inlet left ventricle. In all but one of the patients the loops showed a coordinate phase relation between pressure and volume, and cycle efficiency was similar in the two groups ($p = \mathrm{NS}$) and similar to that measured in the normal left ventricle.[7] In patient 8, who showed profoundly reduced pulmonary blood flow and severe systemic desaturation at catheterisation (oxygen saturation $= 62\%$), the pressure-volume loop showed an abnormal diastolic limb with a much reduced cycle efficiency (45%).

Systolic stroke work, measured by planimetry of the loops, was lower in tricuspid atresia and correlated ($p < 0\cdot05$) with stroke volume and shape change (all patients, $r = 0\cdot73$ and $0\cdot7$ respectively).

Discussion

Infants with univentricular atrioventricular connection account for up to 10% of symptomatic patients presenting with congenital heart disease.[15] In many of these patients the condition can be palliated in early life and later such patients may be suitable for a corrective procedure. The accurate assessment of ventricular function in these patients, both before and after such procedures, is therefore of considerable importance.

Unlike the normal left ventricle, which approximates to a prolate ellipsoid, the left ventricle in these patients may vary considerably in size, shape, and position. Whatever method of measurement is used, these factors are likely to influence the results when assessing ventricular function from angiograms. In particular, the application of algorithms derived for the measurement of normal left ventricular volume from single plane angiograms is not valid. In this study we used a computer assisted method to measure left ventricular volume from biplane angiograms using a modification of Simpson's rule.

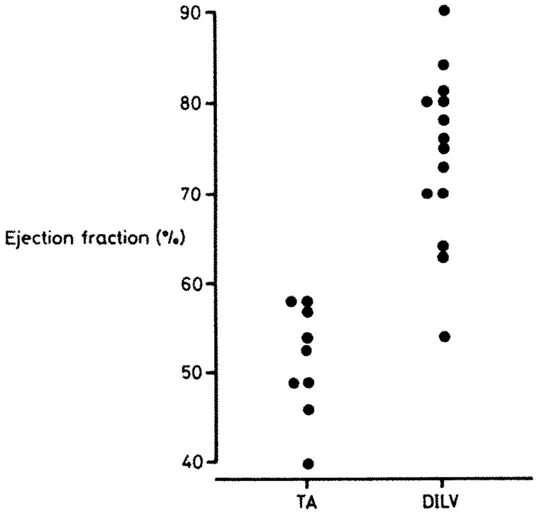

Fig 3 *Left ventricular ejection fraction in tricuspid atresia (TA) compared with double inlet left ventricle (DILV). The ejection fraction was lower in patients with tricuspid atresia.*

Table 3 *Angiographic data on patients with tricuspid atresia or double outlet left ventricle*

Patient	*Age (mth)*	*BSA (m^2)*	*EDVI (ml/m^2)*	*ESVI (ml/m^2)*	*SVI (ml/m^2)*	*EF (%)*	*EDSI*	*ΔSI (%)*	*PFR /EDV*	*tPFR (ms)*	*PER /EDV*	*tPER (ms)*	*SSW ($J/beat/m^2$)*	*RR interval*	*CE*
Double inlet left ventricle															
1	216	1·44	132	40	92	70	89	18	5·3	110	3·2	80	0·92	660	64
2	192	1·41	135	29	106	78	76	20	4·4	50	4·4	110	1·03	580	64
3	121	0·92	138	22	116	84	91	21	3·6	180	4·4	50	1·06	720	72
4	96	0·87	224	80	144	64	76	15	4·1	—	4·1	170	0·79	640	53
5	42	0·6	135	27	108	80	74	18	12·1	20	8·0	80	—	300	—
6	42	0·63	134	31	103	76	76	12	4·6	100	4·0	30	1·20	540	72
7	36	0·58	163	15·5	147·5	90	90	36	8·5	45	6·9	30	1·40	460	81
8	24	0·4	118	35	83	70	80	12	3·8	40	3·5	210	0·28	640	45
9	25	0·51	117	22	95	81	79	10	7·2	90	4·5	60	0·68	560	72
10	22	0·47	141	38	103	73	87	20	5·3	90	5·1	105	0·75	580	62
11	10	0·5	147	36	111	75	78	21	6·1	90	4·1	110	0·87	400	81
12	4	0·24	108	21	87	80	76	24	8·4	100	13·1	100	—	400	—
13	156	1·18	82	30	52	63	76	13	3·3	70	3·2	130	0·40	470	69
14	41	0·58	136	62	74	54	88	9	5·4	80	5·0	50	0·50	410	53
Mean	73		136	45	101	74	81	18	5·9	82	5·2	94	0·82	530	67·5
(SD)	(70)		(32)	(18)	(25)	(9)	(6)	(7)	(2·5)	(40)	(2·6)	(51)	(0·33)	(120)	(9·2)
Tricuspid atresia															
15	42	0·55	153	64	89	58	98	9	6·6	65	4·25	25	0·52	460	55
16	36	0·56	151	63	88	58	90	12	5·0	50	3·0	170	0·84	580	77
17	36	0·54	213	127	86	40	94	0	3·4	50	2·2	150	—	540	—
18	25	0·6	83	38	45	54	84	0	2·7	90	2·5	160	—	640	—
19	98	0·94	101	43	58	57	86	4	4·1	100	3·4	30	0·37	500	59
20	6	0·26	107	54	53	49	88	8	3·7	60	3·3	90	0·26	500	64
21	59	0·81	140	71	69	50	90	3	5·0	90	1·7	120	—	580	—
22	144	1·2	101	54	47	46	78	6	3·3	30	4·7	20	—	500	—
23	51	0·77	108	60	48	46	86	10	3·3	60	5·2	50	0·45	600	66
Mean	55		129	64	65	51	88	5·8	4·1	66	3·4	91	0·48	540	65
(SD)	(42)		(40)	(26)	(19)	(6·5)	(6)	(4·3)	(1·2)	(22)	(1·2)	(61)	(0·22)	(60)	(8)

BSA, body surface area; EDVI, end diastolic volume index; ESVI, end systolic volume index; SVI, stroke volume index; EF, ejection fraction; EDSI, end diastolic shape index, PFR, peak filling rate; tPFR, time to PFR; PER, peak ejection rate; SSW, systolic stroke work; CE, cycle efficiency

This has previously been shown to be an accurate method of volume measurement that overcomes some of the geometric assumptions inherent in single plane derivations. The ventricle is divided into 40 elliptical slices and the major and minor dimensions of these are taken from each of the angiographic views.[12] Several groups have used similar methods and have reported raised ventricular volumes and depressed ejection fraction in patients with tricuspid atresia,[6,16,17] but there have been few attempts to measure more sensitive indices of function or to compare function in these patients with those who have other forms of univentricular atrioventricular connection. Left ventricular end diastolic volume, corrected for body surface area, was similar in our patients with tricuspid atresia and those with double inlet left ventricle. As might be expected, however, the absolute values for end diastolic volume were considerably higher than normal in these ventricles receiving both systemic and pulmonary venous return.[7] The ejection fraction in our patients with tricuspid atresia was similar to that reported with both angiographic[4,17] and radionuclide techniques.[5,18] Unlike other studies, however, we were unable to confirm any significant relation in our small study between ejection fraction and age,[4] previous systemic-to-pulmonary shunt procedures,[6] or systemic oxygen saturation.[17] Indeed the finding of normal, and often supranormal, ejection fraction in the patients with double inlet left ventricle, of similar age range, haemodynamic function, and distribution of previous palliative procedures suggests that these factors may not be primary determinants of the reduced ejection fraction seen in patients with tricuspid atresia.

It is perhaps more likely in the light of our findings that the cause of the reduced ejection fraction in tricuspid atresia is structural. The normal left ventricle ejects a considerable proportion of its stroke volume by an alteration of its shape during systole.[11] In a previous study this normal change in shape seemed to be much reduced in patients with univentricular hearts[19] although in four patients, all with two atrioventricular valves, this change in shape seemed to follow more closely the pattern of the normal left ventricle. In our patients with double inlet left ventricle both the end diastolic shape index and the change in shape index during systole were similar to normal values.[11] In contrast in tricuspid atresia the left ventricle was more globular at end diastole and changed little during systole; thus virtually all the change in cavity volume in these ventricles resulted from myocardial fibre shortening. It is possible that disruption of the normal myocardial fibre architecture, because of the absence of an atrioventricular connection, reduces the ability of the ventricle to change its cavity volume by changing shape. Indeed the ejection fraction and change in shape index were normal in a single patient studied with atrioventricular concordance and an imperforate right atrioventricular valve but otherwise similar haemodynamic function to classic tricuspid atresia (unpublished). The significant linear relation between change of shape and ejection fraction in our patients further supports this concept but cannot exclude a common, unrecognised, aetiological factor.

Frame by frame analysis of ventricular volume shows further differences in both systolic and diastolic indices of function. The peak rate of ventricular filling was significantly lower in patients with tricuspid atresia than in those with double inlet left ventricle. It is clear, however, that peak filling rate is higher in those with a double inlet than previously published normal values.[20] It is possible that peak filling rate is higher than normal in these patients because the ventricle is filling through two atrioventricular valves. There was a significant relation between the RR interval and peak filling rate in the double inlet group ($r = 0{\cdot}73$), however, and it is likely that the increase in peak filling rate was related to the relatively high heart rate in these patients. There was no haemodynamic evidence of inflow obstruction in our patients with tricuspid atresia, either across the atrial septum or across the left atrioventricular valve, and so filling was probably impaired when compared with normal. The time to peak filling rate was also reduced in these patients and this combination of an early yet reduced peak rate of ventricular filling is similar to that seen in adults with a raised end systolic volume and reduced ejection fraction secondary to ischaemic cardiomyopathy.[20]

Despite the abnormalities described above the left ventricular pressure-volume loops showed a coordinate phase-relation between pressure and volume in most patients, and, apart from a single patient with reduced pulmonary blood flow and severe systemic desaturation, the cycle efficiency of the loops was normal. Systolic stroke work, equal to the area enclosed by the pressure-volume loop, was higher in the group with double inlet left ventricle simply because of the higher stroke volume in these patients.

The implications of these findings for corrective or radical palliative surgery are unclear. It has been suggested that normal preoperative ventricular function is an essential prerequisite for the Fontan operation or its modifications.[3] Yet the survival of patients after these procedures appears to be higher in patients with tricuspid atresia than in those with double inlet left ventricle.[8] It seems that in most young patients undergoing Fontan-like procedures preoperative ventricular function is not a primary determinant of survival. It is possible that the influence of preoperative ventricular function will vary depending on the type of atrioventricular connection, however. Furthermore, it is not known how preoperative ventricular function will affect performance in the survivors of these operations. We have increasing evidence that cardiac output and exercise tolerance are reduced after the Fontan procedure[21] but there are little data relating these findings to measurements of preoperative ventricular function. A large scale longitudinal study of these patients would help to answer some of these questions.

Our results show that ventricular function in patients with tricuspid atresia is often worse than in those with double inlet left ventricle. These abnormalities are more likely to be related to structural differences rather than to differences in haemodynamic function or the effects of previous palliative operation. The higher survival after the Fontan operation of patients with tricuspid atresia suggests that ventricular function is not a primary determinant of outcome after this procedure.

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Relation between histological findings on early repeat right ventricular biopsy and ventricular function in patients with myocarditis*

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SUMMARY Histological findings on repeat endomyocardial biopsy and changes in left ventricular ejection fraction early during immunosuppressive treatment were studied in 20 patients with documented myocarditis. All patients presented with heart failure of less than six months' duration and a left ventricular ejection fraction of $\leqslant 0{\cdot}40$. Repeat biopsy and assessment of ventricular function were performed at a mean (SEM) of 79 (17) days after the initial biopsy. At repeat biopsy eight patients had evidence of ongoing myocarditis and 12 showed resolved myocarditis. In eight (66%) of the 12 patients with resolved myocarditis ventricular function had improved significantly. Left ventricular ejection fraction also improved significantly in four of eight patients during treatment despite ongoing myocardial inflammation. Regardless of the histological findings on repeat biopsy, early improvement in ejection fraction was associated with an excellent long term prognosis—that is 83% survived for at least three years.

Histological resolution of myocarditis during immunosuppressive treatment is not a prerequisite for improvement in ventricular function; and changes in left ventricular ejection fraction during the first three months of treatment are predictive of clinical outcome.

Myocarditis can present suddenly as dilated cardiomyopathy.[1 2] Examination of a biopsy specimen of the right ventricular endomyocardium can confirm myocarditis. Although the natural history and treatment of myocarditis remain uncertain,[1-3] observations by Mason *et al* and Daley *et al* suggest that a subset of patients may show both histological and haemodynamic improvement as a result of immunosuppressive treatment.[4 5] Serial biopsy of the right ventricular endomyocardium is often performed to assess the effect of treatment on myocardial inflammation and guide further management. The relation between histological findings and ventricular function during treatment has not been established.

We examined the relation between the histological appearance of the myocardium on repeat endomyocardial biopsy, changes in left ventricular function, and long term clinical outcome in a group of patients with symptomatic heart failure caused by myocarditis.

Patients and methods

PATIENTS

From a review of the medical and pathology records of 637 patients who had undergone right ventricular endomyocardial biopsy between 1 January 1980 and 30 October 1986, we identified 20 consecutive patients who met the following criteria: (*a*) symptomatic heart failure lasting $\leqslant$ 6 months; (*b*) a left ventricular ejection fraction $\leqslant 0{\cdot}40$ by radioventriculogram; (*c*) histological confirmation of myocarditis on initial right ventricular biopsy; (*d*) repeat biopsy and assessment of left ventricular function by radioventriculogram after the start of immunosuppressive treatment.

In all cases, the clinician had requested the initial right ventricular biopsy for diagnostic purposes; the timing of biopsy relative to the duration of the patient's illness was determined only by the timing of this referral. Coronary angiography, performed in all patients, showed no significant obstructive lesions.

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TECHNIQUE OF TRANSVENOUS ENDOMYOCARDIAL BIOPSY AND PATHOLOGICAL EXAMINATION

Right heart catheterisation was performed in all patients on at least two occasions with a triple lumen thermodilution catheter. A biopsy specimen of the endocardium was obtained after the haemodynamic measurements. We used a technique that resembled earlier descriptions.[2 6] Multiple biopsy samples (usually 4–7, each measuring 1–2 mm in diameter) were taken from the right ventricular septum by means of a Caves-Schultz-Stanford bioptome inserted through the right internal jugular vein. Biopsy samples were processed according to standard staining and embedding methods.[2]

Biopsy specimens were classified on the basis of a review of all light microscopic slides, including plastic thick sections and frozen section tissue slides. Myocarditis was diagnosed on initial biopsy if there was a lymphocytic infiltrate, either focal or diffuse, in association with necrotic or degenerating myocytes.[7] All repeat biopsy specimens were compared with that individual's initial biopsy specimen and were then classified according to the Dallas criteria[7] into one of three categories:

(*a*) *Ongoing myocarditis.*—Specimens continued to show evidence of a persistent inflammatory infiltrate and ongoing degeneration or necrosis of adjacent myocytes.

(*b*) *Resolving myocarditis.*—Specimens showed continued cellular inflammation but no evidence of myocyte necrosis. The inflammatory infiltrate, although present, had decreased in amount.

(*c*) *Resolved myocarditis.*—These biopsy specimens showed resolution of both infiltrate and myocyte necrosis.

Each biopsy specimen was also graded for the degree of fibrosis according to the following semiquantitative scale: 0, no fibrosis; 1+, focal fibrosis; 2+, multifocal interstitial fibrosis; and 3+, diffuse interstitial or replacement fibrosis. The patients were then divided into two groups on the basis of histological findings on repeat biopsy: ongoing: myocarditis (including resolving histology) and resolved myocarditis.

ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND CLINICAL STATE

At initial and follow up assessment the left ventricular ejection fraction was measured by multiple gated equilibrium radioventriculography.[8] Right ventricular ejection fraction was measured in one patient with isolated right heart failure who had normal left ventricular function by first pass radioventriculogram. All ventriculograms were obtained within 14 days of the repeat right ventricular biopsy and most were performed the same day. Left ventricular function was considered to have improved during treatment if the left ventricular ejection fraction on the repeat ventriculogram had increased by > 0·10.

We also reviewed the medical records and questioned each patient about the severity of their symptoms and functional limitations caused by congestive heart failure. On the basis of information, each patient was assigned a New York Heart Association classification at the time of initial presentation, follow up biopsy, and most recent clinical evaluation. Clinical improvement was defined as: (*a*) a decrease in symptomatic heart failure by one or more New York Heart Association classes in association with (*b*) a rise in ventricular ejection fraction by ⩾ 0·10.

TREATMENT PROTOCOLS

All patients presented with symptomatic heart failure and had been receiving digoxin and diuretic treatment at the time of initial biopsy. Most patients were also receiving vasodilators (captopril or prazosin). Patients were given optimal medical treatment for heart failure before the initial measurement of ventricular function and treatment was not increased between the initial and follow up studies. Systemic anticoagulation and antiarrhythmic agents were used according to standard clinical indications.

All 20 patients were given immunosuppressive agents and underwent repeat biopsy during treatment as part of our routine treatment protocol. Prednisone was administered at an initial dose of 1·25 mg/kg/day for the first week. The dose was then tapered to 0·33 mg/kg/day by the end of the twelfth week. The dosage remained constant for an additional eight weeks and was then tapered to zero by the end of week 24. One patient did not consent to treatment with azathioprine. The remaining 19 patients were given azathioprine at a dose of 2 0 mg/kg/day for the entire six months of treatment, unless leucopenia (white blood cell count < 5000/ml) developed.

STATISTICAL ANALYSIS

Statistical analyses were performed by RS/1 (Bolt Beranek and Newman) COMPARE. A p value of < 0·05 was regarded as statistically significant for a single set of data. All group data were expressed as the mean (SEM).

Results

The table shows the radioventriculographic, clinical, and histological characteristics of the 20 patients (mean age 45·8 (3·1) years) with myocarditis. Biventricular heart failure was present in all but one patient, who had predominantly right ventricular dysfunction. The mean initial group ejection fraction was 0·22 (0·02) (range 0·07–0·40) and New York Heart Association class was 3·7 (0·1). Repeat right ventricular biopsy was performed 79 (17) days (range 20–338) from initial sampling. The mean ventricular ejection fraction at the time of follow up examination had increased to 0·35 (0·03) (range 0·18–0·58) ($p = 0·0005$) and the New York Heart Association class had decreased to 2·0 (0·2) ($p \leqslant 0·01$).

HISTOLOGICAL FINDINGS AND VENTRICULAR FUNCTION

The table shows the changes that we saw in left ventricular function during immunosuppressive treatment in each patient. Doses of diuretic and vasodilators were either unaltered or reduced between the initial and follow up assessments of ventricular function (data not shown). The individual response to immunosuppressive treatment was highly variable. Left ventricular function improved in 12 (60%) patients and remained unchanged or declined in eight patients. Figure 1 shows the change in ventricular ejection fraction for each patient by histological classification on repeat biopsy. Eight patients had ongoing myocarditis and in 12 patients histological examination showed resolved myocarditis. The timing of follow up biopsy and radioventriculographic measurement of ventricular function did not differ between the two histological groups: group with ongoing myocarditis 86 (21) days *v* group with resolved myocarditis 75 (25) days ($p > 0·05$). Improvement in systolic ventricular performance was independent of myocardial inflammation on repeat biopsy and occurred in four of eight patients with ongoing myocarditis compared with eight of 12 (66%) patients with resolved myocarditis. The mean ejection fraction for the group with resolved myocarditis increased from 0·20 (0·02) to 0·35 (0·05) ($p = 0·001$) while that of the group with ongoing myocarditis rose from 0·25 (0·03) to 0·34 (0·04) ($p = 0·03$).

The degree of fibrosis seen on initial and follow up endomyocardial biopsy was also measured and analysed to determine its effect on changes in ventricular function. Initial biopsy showed no fibrosis in seven (35%) patients, focal or multifocal fibrosis in nine (45%), and diffuse interstitial or replacement fibrosis in the remaining four patients. The fibrosis scores in the groups with ongoing and resolved myocarditis were 1·4 (0·4) and 1·2 (0·3) respectively at initial biopsy and 1·4 (0·5) *v* 1·0 (0·3) at follow up biopsy. The extent of fibrosis on initial or repeat biopsy did not correlate with changes in ejection fraction.

CLINICAL IMPROVEMENT AND OUTCOME

Clinical improvement (a decrease in New York Heart Association symptom class and a rise in ventricular ejection fraction) was a common finding during the treatment for myocarditis. Improvement was seen in seven (58%) of 12 of the patients with resolved myocarditis and in four of eight with ongoing myocarditis ($p =$ NS). Not surprisingly, an improvement in symptoms was more common when

Table *Histological, haemodynamic, and clinical characteristics of 20 patients with treated myocarditis*

			Ejection fraction		*NYHA class*			*Fibrosis score*			*Follow up*	
Case	*Age*	*Sex*	*Initial*	*Follow up*	*Initial*	*Follow up*	*Interval between biopsies (days)*	*Initial*	*Follow up*	*Repeat biopsy histology*	*Duration (days)*	*Clinical outcome*
1	42	F	0·40*	0·50*	III	II	62	2+	3+	Ongoing	2209	A (II)
2	45	M	0·13	0·43	IV	I	205	0	2+	Ongoing	1188	A (I)
3	32	M	0·19	0·30	IV	II	62	3+	0	Ongoing	302	D
4	52	F	0·37	0·34	IV	IV	134	3+	3+	Ongoing	156	D
5	28	M	0·24	0·20	IV	III	44	0	0	Ongoing	1124	D
6	46	M	0·19	0·20	IV	II	40	0	1+	Ongoing	1084	T
7	58	F	0·26	0·34	III	III	30	2+	2+	Ongoing	583	D
8	64	F	0·27	0·44	IV	I	111	1+	0	Ongoing	712	A (I)
9	22	M	0·14	0·18	IV	IV	23	2+	0	Resolved	529	T
10	45	M	0·07	0·30	IV	I	26	0	1+	Resolved	1643	A (I)
11	50	M	0·10	0·30	IV	I	64	0	1+	Resolved	1233	A (I)
12	64	F	0·23	0·16	III	II	28	0	3+	Resolved	1209	A (II)
13	31	M	0·13	0·13	IV	IV	29	1+	0	Resolved	79	D
14	19	M	0·20	0·49	II	II	20	3+	3+	Resolved	1073	T
15	70	F	0·24	0·24	II	II	338	0	0	Resolved	1097	A (II)
16	57	M	0·20	0·51	III	I	97	1+	1+	Resolved	783	A (I)
17	45	F	0·34	0·55	IV	I	84	1+	1+	Resolved	664	A (I)
18	49	F	0·25	0·58	IV	I	72	2+	1+	Resolved	226	A (I)
19	47	F	0·20	0·30	IV	I	82	1+	1+	Resolved	327	A (I)
20	49	F	0·27	0·51	IV	II	33	3+	0	Resolved	334	A (III)

*Right ventricular ejection fraction

NYHA, New York Heart Association.

0, no fibrosis; 1+, focal interstitial fibrosis; 2+, multifocal interstitial fibrosis, 3+, diffuse interstitial or replacement fibrosis.

A, alive (New York Heart Association class I–IV), D, died; T, cardiac transplantation.

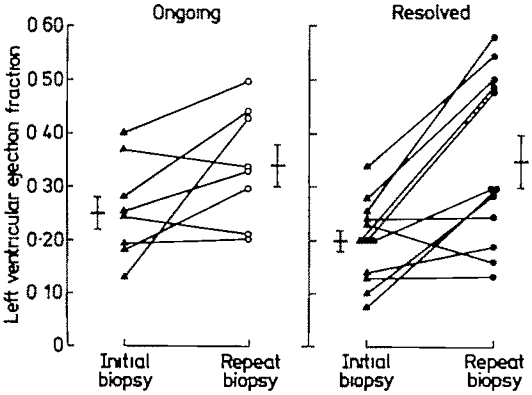

Fig 1 *Left ventricular ejection fraction for each patient at initial and repeat biopsy. Patients are grouped according to histological findings on repeat biopsy.*

the ventricular ejection fraction increased. Eleven of the 12 patients who showed a substantial increase in ejection fraction had a decline in New York Heart Association class. The one patient (case 14) whose symptoms did not improve despite an increase in left ventricular systolic performance had only mild (class II) symptoms at the time of both initial and follow up evaluations.

Clinical improvement after completion of six months of immunosuppressive treatment was highly dependent upon changes in ventricular function rather than on histological findings on repeat endomyocardial biopsy. In 12 patients the ejection fraction improved during treatment from 0·22 (0·03) to 0·43 (0·03); $p < 0·05$) and all were alive one year after initial biopsy. Repeat biopsy showed resolved myocarditis in eight patients and ongoing myocarditis in the remaining four. Fibrosis was either absent or focal in nine of these 12 patients and the fibrosis score for the group was 1·2 (1·0). Although serial assessments of ventricular ejection fraction and myocardial histology were not available for every patient, complete clinical follow up was collected. The mean duration of clinical follow up for the group showing an improvement was 891 (175) days (range 226–2209 days). Ten patients are alive. In one patient left ventricular function gradually declined and he died of sepsis. Refractory myocarditis developed in the other individual who underwent cardiac transplantation. The mean New York Heart Association class for the group improved from a mean value of 3·7 (0·2) at initial biopsy to 1·3 (0·1) ($p < 0·05$) at the time of repeat biopsy. This improvement in functional capacity was sustained after the end of immunosuppressive treatment, as shown by a mean New York Heart Association class of 1·7 (0·3) at the time of most recent clinical evaluation (fig 2). Of the 10 surviving patients, eight remain in class I.

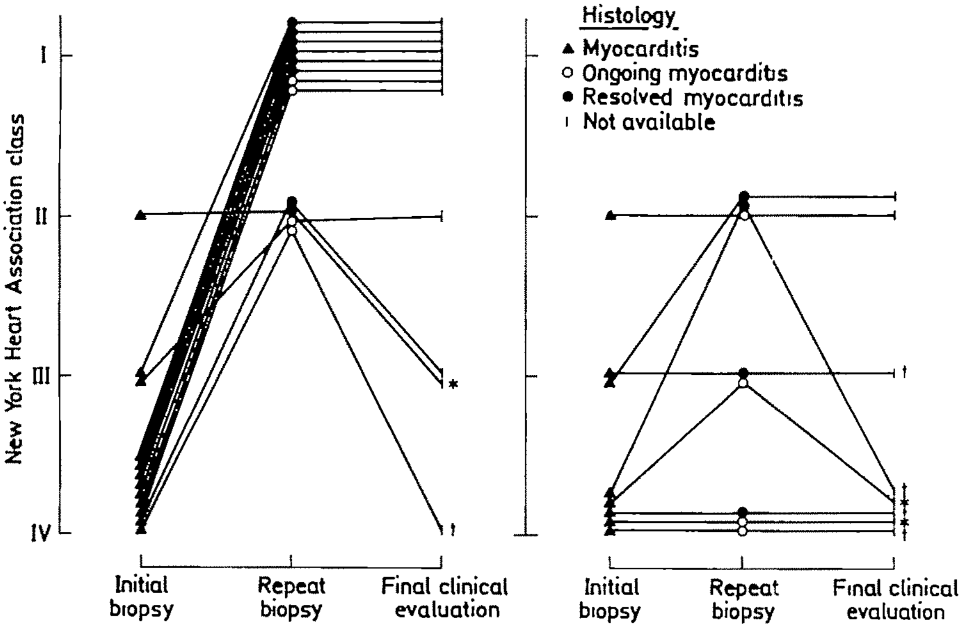

Fig 2 *New York Heart Association classification for each patient at the time of initial biopsy, repeat biopsy, and final clinical assessment. Patients are grouped by improvement or lack of improvement in left ventricular ejection fraction (LVEF) at the time of repeat biopsy. Improvement was defined as an increase in LVEF of ≥ 0·10.*

Ventricular function did not improve early during immunosuppressive treatment in eight patients (0·22 (0·03) to 0·22 (0·03)). Clinical follow up for this group averaged 732 days (range 79–1209). Histological findings on repeat biopsy showed ongoing myocarditis in four patients and resolved myocarditis in the remaining four. Fibrosis on both initial and repeat biopsy was generally focal and fibrosis scores resembled those in the improved group. Two patients died of progressive heart failure in the first year after initial biopsy. Two additional patients died during the second year, while two others underwent cardiac transplantation for refractory heart failure. Only two non-transplanted patients are alive and both have considerable functional limitations (New York Heart Association class III). The mean class at the time of initial biopsy, repeat biopsy, and final determination either before death or transplantation or during most recent clinical evaluation was 3·5 (0·03), 3·0 (0·03, and 3·4 (0·03) (p = NS) respectively (fig 2).

Discussion

Although endomyocardial biopsy has shown that myocarditis is associated with acute cardiac dilatation and symptomatic heart failure,[9–11] both the prognosis and the most effective treatment remain uncertain. Uncontrolled observations[4 5 12] have suggested that immunosuppression may be of benefit in certain individuals, but no randomised clinical trial has yet been completed. In the absence of this information, a growing number of patients are now being treated with immunosuppressive agents once myocarditis has been histologically confirmed. The most effective method of monitoring the effects of treatment in patients with myocarditis is as controversial as the type of treatment used. Most centres that use immunosuppressive agents routinely perform repeat endomyocardial biopsy within 12–16 weeks of the start of treatment. Although immunosuppressive agents can reduce or eliminate lymphocytic inflammation and myocyte necrosis within several months, resolution can be spontaneous.[13–15] Most (60%) patients in our study showed resolved myocarditis at repeat biopsy after an average of 11 weeks of immunosuppressive treatment. None the less, these histological findings correlated poorly with changes in left ventricular ejection fraction and functional state. Left ventricular function improved and symptoms decreased in four of eight patients with histological evidence of ongoing myocarditis and in 60% of those individuals with resolved myocarditis.

It is not entirely surprising that histological and haemodynamic improvements do not parallel one another. There are several explanations for this apparent discrepancy. One possibility is that the transvenous biopsy technique does not provide a representative histological picture of either the degree of ongoing inflammation or interstitial fibrosis in a disease that is often focal or multifocal.[16] Many patients who seemed to have resolved myocarditis may have had other areas of myocardial inflammation and myocyte necrosis that were undetected on repeat biopsy. It is also possible that those patients who did not improve had a greater degree of fibrosis and irreversible ventricular dysfunction before the start of treatment. This explanation seems unlikely since both the initial fibrosis score and ejection fraction were similar in the two groups. Another explanation is that the histological findings obtained from right ventricular biopsy do not reflect the events that occur in the left ventricle during myocarditis, where the haemodynamic dysfunction has most effect. This explanation remains possible, although unlikely, because previous pathological studies have confirmed that right ventricular sampling is representative of left ventricular histological findings in most cases of myocarditis.[17]

Another possibility is that those patients with ongoing myocarditis presented earlier in their illness and were treated before the development of permanent left ventricular dysfunction. While all patients reported heart failure symptoms lasting < 6 months, and the interval between the development of symptoms of heart failure and initial right ventricular biopsy did not appear to be shorter in the group with ongoing myocarditis, this possibility cannot be excluded because the duration of illness was based upon the patient's subjective estimation of the onset of symptoms.

CLINICAL IMPROVEMENT AND OUTCOME

During treatment with prednisone alone or with azathioprine both ventricular function and clinical symptoms improved in approximately 60% of individuals with symptomatic heart failure of recent onset caused by myocarditis. These findings confirm previous biopsy studies[4 12 14] and uncontrolled observations in a larger series of our own patient population and suggest that a subset of patients may improve as the result of immunosuppression.

While no relation was seen between changes in ventricular function during treatment and the presence or absence of myocardial inflammation on repeat endomyocardial biopsy, a substantial rise in ejection fraction within the first three months of immunosuppressive treatment was predictive of sustained improvement in functional state. Ten of the 12 patients who showed early improvement in ventricular function are alive, and all but two are in New York Heart Association class I. This contrasts with the eight patients who did not show an early improvement in ejection fraction during treatment.

Six of them have died or undergone cardiac transplantation for progressive heart failure, while the remaining two patients continue to experience considerable functional limitations. While several patients who improved did eventually show clinical deterioration and worsening symptoms during long term follow up, perhaps because of reactivation of myocarditis, patients who did not show an improvement in symptoms and functional class at the time of repeat biopsy and clinical assessment did not do so later.

These findings are similar to a smaller series recently reported by Quigley *et al* which showed that an improvement in ventricular function within 6–8 months of immunosuppressive treatment for myocarditis was highly predictive of an excellent long-term prognosis.[18] Further, their study also supports our observation that neither the presence of myocardial inflammation nor the degree of fibrosis on repeat biopsy was predictive of functional improvement. The present study suggests that patients with an excellent prognosis can be identified by changes in left ventricular ejection fraction as early as three months after the start of treatment.

But not all patients who improved during this study did so as a direct result of immunosuppressive treatment. Spontaneous improvement in ventricular function has already been reported.[14] At present those patients who will experience spontaneous symptomatic and haemodynamic improvement cannot be distinguished from those in whom immunosuppressive treatment may be of substantial benefit. We did not attempt to determine the role of immunosuppression in the treatment of myocarditis and there was no randomised control group in our study.

We examined only the relation of histological findings during treatment and changes in ventricular function *early* during the course of immunosuppressive treatment. Therefore, although clinical outcome and functional class were followed over many months, we did not obtain serial biopsy specimens or measure ejection fraction after the end of immunosuppressive treatment. We do not know whether continued myocardial inflammation is compatible with a sustained improvement in ventricular performance over the course of many months or years, though this seems unlikely. Finally, it does not seem prudent to recommend alteration in immunosuppressive treatment early during the course of treatment on the basis of the presence or absence of ongoing myocardial inflammation on repeat biopsy.

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Benefits of dual chamber pacing in sick sinus syndrome

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SUMMARY The effects of DDD (fully automatic) and VVI (ventricular demand) pacing modes on exercise tolerance, symptom diary cards, and Holter monitoring were investigated in a randomised double blind crossover study of 16 patients who had had DDD pacemakers implanted because of frequent syncope. Eight patients presented with sick sinus syndrome and, with one exception, retrograde atrioventricular conduction and eight age and sex matched patients presented with 2:1 or complete atrioventricular block. Maximal symptom limited exercise in those with atrioventricular block was significantly higher after one month of DDD pacing than after VVI pacing. In those with sick sinus syndrome, however, maximal effort tolerance was not significantly different for the two pacing modes. In all but one patient with sick sinus syndrome sinus rhythm developed during exercise in VVI pacing. For both VVI and DDD modes maximal atrial rates were significantly lower in those with sick sinus syndrome. Palpitation and general wellbeing were significantly improved during DDD pacing in the eight patients with sick sinus syndrome. Shortness of breath was improved by DDD pacing in the eight patients with atrioventricular block but not in those with sick sinus syndrome. Holter monitoring showed that sick sinus syndrome patients remained in paced rhythm, either DDD or VVI, for most of the 24 hour period.

DDD pacing was better than VVI pacing in sick sinus syndrome with retrograde atrioventricular conduction. Despite their ability to show sinus rhythm and inhibit their pacemakers on exercise patients with sick sinus syndrome are just as likely to have symptomatic benefit from DDD pacing as patients with atrioventricular block.

The availability of a reliable endocardial atrial lead[1-3] led to the development of "physiological" pacemakers that restore the normal activation sequence of atrial contraction followed by ventricular systole and that also permit a physiological increase in heart rate when the sinus rate increases.

Atrial demand pacemakers (AAI) were introduced as a physiological system for patients with sick sinus syndrome. They offered the same advantages as DDD (fully automatic) pacemakers but could not pace the ventricle if a fault developed in atrioventricular conduction. Subsequent development of atrioventricular block, carotid sinus hypersensitivity, and chronic atrial fibrillation made many of these patients unsuitable candidates for AAI pacing[4 5]; however, not every study reported this problem.[6 7] A recent review of the course of sick sinus syndrome suggests that those concerns are real.[8] Atrial synchronous ventricular pacing (VAT, VDD) was unsuitable for patients with sick sinus syndrome because of the potential for persistent bradycardia which causes these units to pace in VVI mode at low rate. An atrioventricular sequential pacemaker (DVI) can be used for patients with sick sinus syndrome; however, Furman and Cooper[9] reported a high incidence of atrial fibrillation with DVI pacing, possibly because of competition with atrial activity which is not sensed in this mode. Thus DDD appears to be an appropriate semi-physiological pacing mode for patients with sick sinus syndrome. This type of unit does not correct for the lack of ability of the sinus node to increase its rate normally on exercise. A future generation of DDD pacemakers will have an additional physiological sensor (other than the P wave) to offer this correction.

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Retrograde atrioventricular conduction is preserved in most patients with sick sinus syndrome who have intact atrioventricular conduction.[10 11] Pacemaker syndrome develops when atrioventricular synchrony is lost during VVI (ventricular demand) pacing with or without retrograde atrioventricular conduction.[12 13] Recent studies have emphasised the relation between preserved retrograde atrioventricular conduction and the development of pacemaker syndrome.[14 15] Because of preservation of retrograde atrioventricular conduction, patients with sick sinus syndrome and without atrioventricular block potentially are at more risk of pacemaker syndrome if paced in the VVI mode than patients with intermittent or complete anterograde atrioventricular block, in which retrograde atrioventricular conduction is also compromised. Despite this, VVI pacing has been frequently used for sick sinus syndrome patients.

This is the first study to compare (*a*) exercise tolerance and symptoms in DDD and VVI modes in sick sinus syndrome, (*b*) the effects of DDD pacemakers in patients with sick sinus syndrome and in sex-matched patients with atrioventricular block, and (*c*) the frequency of cardiac arrhythmias during DDD and VVI modes during Holter monitoring of patients with sick sinus syndrome.

Patients and methods

PATIENT SELECTION

We studied 16 patients who had had mode programmable DDD pacemakers implanted at least three months before the study. At the time of the study none of the patients had severe physical disability (for example, arthritis or stroke). Table 1 shows the clinical details. All patients were assessed by prepacing electrophysiological studies including measurement of intervals on His bundle electrograms, estimation of sinus node recovery times (for atrial pacing rates between 90 and 220 beats/min), incremental atrial pacing for assessment of Wenckebach cycle length and change of His-ventricular time, assessment of retrograde atrioventricular conduction for ventricular pacing rates of 80–160 beats/min, and observation of the effects of carotid sinus massage on sinoatrial activity and atrioventricular conduction.

Eight patients had sick sinus syndrome (group 1) and eight had atrioventricular block (group 2). The two groups were age and sex matched. All presented with frequent presyncope and syncope.

There was only one woman in group 1 (mean age 64·1 years (range 41–75)). All had symptomatic sick sinus syndrome, diagnosed electrocardiographically

Table 1 *Patient data*

					Prepacing electrophysiological data				
Case No	*Age/sex*	*Other clinical diagnosis*	*Prepacing symptom*	*ECG findings*	*Sinus cycle length (ms)*	*CSNRT (ms)*	*VA conduction and interval (ms)*	*Months since implant*	*Daily drug treatment*
Group 1 (SSS)									
1	75 M	None	Syncope	SB	1400	2260	240	48	—
2	74 M	None	Syncope	BTS, LBBB	1150	650	250	39	—
3	73 M	None	Syncope	BTS, CRBBB	1020	570	200	21	—
4	71 M	None	Dizziness	SA or SAB	1330	5400	—	5	—
5	68 M	None	Syncope	BTS	950	430	190	14	—
6	57 M	HT	Syncope	SA or SAB	1880	2720	220	10	Nifedipine (40 mg)
7	54 M	None	Syncope	SA or SAB	1030	290	240	14	—
8	41 F	None	Dizziness	SA or SAB	990	870	250	7	—
Mean (SD)	64 1 (12 2)				1219 (313)	1649 (1760)	227 (24)	20 (16)	
Group 2 (AVB)									
9	75 M	AP	Dizziness	CHB	620	370	—	36	Nifedipine (20 mg)
10	72 M	OMI	Syncope	CHB	590	430	—	20	Nifedipine (30 mg) Metoprolol (100 mg)
11	72 M	None	Syncope	CHB	710	400	—	23	—
12	69 M	None	Syncope	CHB	830	520	—	34	—
13	67 M	None	Dizziness	CHB	600	430	—	28	—
14	62 M	OMI	Syncope	CHB	750	450	—	34	Metoprolol (100 mg)
15	55 M	AP	Syncope	2 1 AVB	740	330	—	17	—
16	35 F	None	Dyspnoea	CHB	560	310	—	20	—
Mean (SD)	63 3 (13 1)				675 (96)	405 (68)		27 (7)	

ECG, electrocardiographic, CSNRT, corrected sinus node recovery time; VA, ventriculoatrial· SSS, sick sinus syndrome, SB, sinus bradycardia, BTS, bradycardia-tachycardia syndrome, LBBB, left bundle branch block, CRBBB, complete right bundle branch block; SA, sinus arrest, SAB, sinoatrial block, HT, hypertension, AVB, atrioventricular block, AP, angina pectoris; CHB, complete heart block, OMI, old myocardial infarction.

by persistent resting sinus bradycardia (rate <55 beats/min), sinus arrest, and sinoatrial block by conventional electrocardiography and 24 hour Holter recordings. All had evidence of chronotropic incompetence (maximal rate at maximum exercise <120 beats/min). Seven of the eight patients with sick sinus syndrome had retrograde atrioventricular conduction. The aetiology was unknown in all group 1 patients. None had symptoms or signs of heart failure.

There were also seven men and one woman in group 2 (mean age 63·3 years (range 35–75)). All had symptomatic persistent 2:1 or complete atrioventricular block. No patients in group 2 had retrograde atrioventricular conduction, but four had ischaemic heart disease (two with previous myocardial infarction and two with angina of effort).

Patients had had their pacemaker implanted in DDD mode for a mean of 23 months (group 1, 20 months; group 2, 27 months) before entry into the trial to ensure that they were haemodynamically stable at entry.

TRIAL PROTOCOL

The trial was designed as a within patient double blind prospective study of symptoms and exercise tolerance between the two pacing modes with sufficient time in each mode to permit adaptation. Patients were investigated as outpatients. All patients were programmed in DDD mode before the trial began. We asked patients to keep diary cards of their symptoms for two consecutive months, and a Holter 24 hour period was recorded (sick sinus syndrome patients only) and a maximal stress test was performed at the end of each study period. During the first month the pacemaker mode was randomly programmed to either the VVI or DDD mode. For the second month the alternative mode was programmed. Table 2 shows the sequence of modes for each patient.

Table 2 *Sequence of pacing modes*

Case No	*First month**	*Second month*
Group 1 (SSS):		
1	DDD	VVI
2	VVI	DDD
3	VVI	DDD
4	DDD	VVI
5	DDD	VVI
6	DDD	VVI
7	VVI	DDD
8	VVI*	DDD
Group 2 (AVB):		
9	VVI	DDD
10	VVI	DDD
11	DDD	VVI†
12	DDD	VVI
13	DDD	VVI
14	DDD	VVI
15	DDD	VVI
16	VVI	DDD

*14 days in VVI mode; †three days in VVI mode.
SSS, sick sinus syndrome; AVB, atrioventricular block.

At the end of each study month patients performed a symptom limited maximum exercise stress test on an electrically braked bicycle ergometer (Siemens Elema). Before entry to the trial patients also had two exercise stress tests to familiarise themselves with the bicycle ergometer and to eliminate a training effect. Exercise was started for a minimum of three minutes at 35 W and continued to maximum capacity with 35 W increases in workload every three minutes. We recorded the total workload achieved (in Watts). Blood pressure was recorded by conventional mercury sphygmomanometer and heart rate was recorded on a three lead electrocardiograph. Blood pressure and heart rate were recorded on the bicycle before exercise, at the end of every three minute stage, and every two minutes for 10 minutes after exercise.

Patients with sick sinus syndrome (group 1) also had 24 hour Holter monitoring by Oxford Medilog (Oxford Medical Instruments) at the end of each month. Bipolar electrocardiographic chest leads were fixed to the chest at the V1 and V6 positions. All electrograms were recorded for 24 hours while patients were ambulant at home and at work. Patients kept a diary card throughout the recording period. The electrocardiographic tape recordings were printed by fibreoptic printer (Oxford Medical Instruments) at a paper speed 25 mm/s. The electrocardiographic pattern was sampled over every first and thirty first minute each hour to measure the mean heart rate, diurnal variation of heart rate, and use of the pacemaker. If atrial arrhythmia was present during the observation minute, the rate was not included in the analysis.

Mean heart rate was defined as the average heart rate during Holter recording. Diurnal variation of heart rate was assessed by comparing the average heart rate at night (from 1 to 4 am) with the average heart rate by day (from 1 to 4 pm). We defined pacemaker use as the percentage of beats recorded while the atrial, atrioventricular sequential, or ventricular modes were operating. Atrial synchronous pacing (VDD mode of operation) was considered as sinus-like activity. We defined maximum heart rate as the fastest sinus rate. If the sinus rate did not exceed the pacemaker back up rate, the back up rate was taken as the maximum heart rate.

We also analysed the incidence and frequency of cardiac arrhythmias. We measured the duration of paroxysmal atrial fibrillation (fibrillation of more than 5 consecutive beats) and we used the following identification criteria to measure extrasystoles (*a*) configuration differing from the regular QRS or pacemaker induced complexes; (*b*) wide complexes (>0·12 s); (*c*) no preceding P wave; (*d*) prematurity. Frequency was calculated as the number of extrasystoles per 1000 complexes.

We also assessed pacemaker mediated tachycardia. Pacemaker mediated tachycardia was defined as a tachycardia associated with dual chamber sensing pacemakers, which detect a retrograde P wave and conduct anterogradely through the pacing system to trigger another ventricular stimulus and thus perpetuate the tachycardia.

In the VVI mode the rate was set at 70 beats/min. In DDD mode the back up low rate was 60 beats/min and the upper P-synchronous rate was 150 beats/min, with an A-V interval of 150 ms and Wenckebach upper rate behaviour. Neither the patient nor the observer of the exercise test were aware of the programmed mode. The observer also performed the statistical analysis while still blind to the pacemaker mode. Pacemaker programming and electrocardiographic monitoring during exercise testing were performed by SLC, who did not perform the subsequent analysis.

The patients kept a daily diary card of symptoms, which had been used in a previous study.[16] They were asked to record the number of attacks of shortness of breath, chest pain, dizziness, palpitation, and syncope that they experienced each day. At the end of each month the patients were also asked to give a subjective score to the following symptoms by comparing them with the previous month: chest pain, dizziness, shortness of breath, palpitation, and general wellbeing. The scores were 1, much worse; 2, a little worse; 3, no change; 4, a little improved; 5, much improved. The program mode used for each month was not known by either the patient or the observer who performed the analysis of the record card data.

STATISTICAL METHODS

We used Student's paired *t* test to compare maximal effort tolerance and atrial rate at rest and peak exercise. We compared these three variables and heart rate changes during Holter monitoring in groups 1 and 2 by an unpaired *t* test. Symptoms that were expressed as number of attacks per week for each month and the monthly symptom scores and the duration of arrhythmias were compared by Wilcoxon's ranked sum test. We compared symptom variables between groups 1 and 2 by Mann-Whitney U test. Results (mean (SD)) with a p value of <0·05 were regarded as significant.

Results

GENERAL

Two patients (8 and 11) had pronounced symptoms in VVI mode and were unable to complete the trial period. They were reprogrammed to DDD at 14 and

Table 3 *Monthly symptom scores for shortness of breath and general wellbeing with total workload achieved in VVI and DDD modes together with atrial rates at rest and maximum atrial rates*

	Effort tolerance (W)		*Atrial rate at rest (bpm)*		*Maximum atrial rate (bpm)*		*Symptom score "shortness of breath"*		*Symptom score "general wellbeing"*	
Case No	*DDD*	*VVI*	*DDD*	*VVI*	*DDD*	*VVI*	*DDD*	*VVI*	*DDD*	*VVI*
Group 1 (SSS):										
1	420	290	60	70	71	70	3	1	3	1
2	520	490	68	70	105	88	3	3	3	2
3	750	685	62	70	111	115	3	3	3	3
4	470	445	60	61	127	100	3	3	3	3
5	570	815	68	71	130	115	3	1	3	2
6	1265	1265	60	70	96	93	3	3	3	2
7	1183	1010	73	70	136	120	5	1	5	1
8	268	273	80	90	136	139	4	1	3	2
Mean (SD)	681 (363)‡	659 (353)‡	66 (7)‡	72 (8)‡	114 (23)‡	105 (22)‡	3·37 (0·74)‡	2·0 (1·06)‡	3·25 (0·7)*	2·0 (0·75)*
Group 2 (AVB):										
9	620	462	78	95	162	162	4	2	4	2
10	718	695	93	88	150	142	3	2	2	3
11	470	268	68	88	136	125	5	1	5	1
12	396	338	78	68	125	109	3	2	3	2
13	567	490	100	96	130	142	3	2	3	2
14	420	320	83	68	120	115	4	1	4	2
15	1010	880	88	90	136	130	3	3	3	3
16	570	420	88	107	142	142	3	2	4	2
Mean (SD)	596 (198)†	484 (207)†	85 (10)‡	88 (14)‡	138 (14)‡	133 (17)‡	3·5 (0·75)*	1·87 (0·64)*	3·5 (0·92)*	2·12 (0·64)*
Group 1 *v* Group 2	‡	‡	‡	‡	*	*	‡	‡	‡	‡

*p<0·05, †p = 0·001, ‡p = NS.

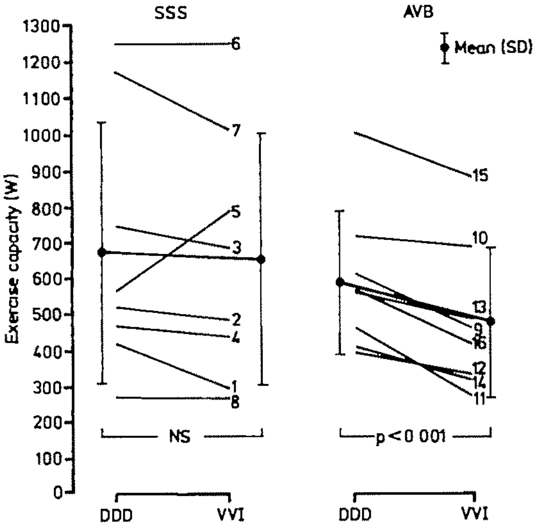

Fig 1 *Maximum effort tolerance in DDD and VVI pacing modes in eight patients with sick sinus syndrome and eight patients with atrioventricular block.*

three days respectively after exercise tests in VVI mode.

EXERCISE TESTS

All but two patients stopped the exercise test because of fatigue or shortness of breath. No patient had ventricular tachycardia or hypotension during exercise. In DDD mode, patients 10 and 14 (both with atrioventricular block) stopped exercising because of chest pain. In both cases, patients completed a repeat exercise test within four days and on this occasion both tests were terminated because of fatigue. Data from second tests were used in the analyses.

All patients with sick sinus syndrome, with the exception of patient 1, developed sinus rhythm during exercise in both DDD and VVI modes. Patient 1 showed atrioventricular sequential or ventricular pacing even at peak exercise. In patients with sick sinus syndrome there was no significant difference in maximal effort tolerance between DDD and VVI modes (681 (363) *v* 659 (353) W) (fig 1 and table 3). On the other hand, in patients with atrioventricular block the maximal effort tolerance achieved in DDD mode was 23% higher than that achieved in the VVI mode (596 (198) *v* 484 (207) W, p = 0·001). No patient with atrioventricular block developed intermittent anterograde atrioventricular conduction during stress testing.

The maximal effort tolerance in the DDD mode was higher (but not significantly) in patients with sick sinus syndrome than in those with atrioventricular block (681 (363) *v* 596 (198) W).

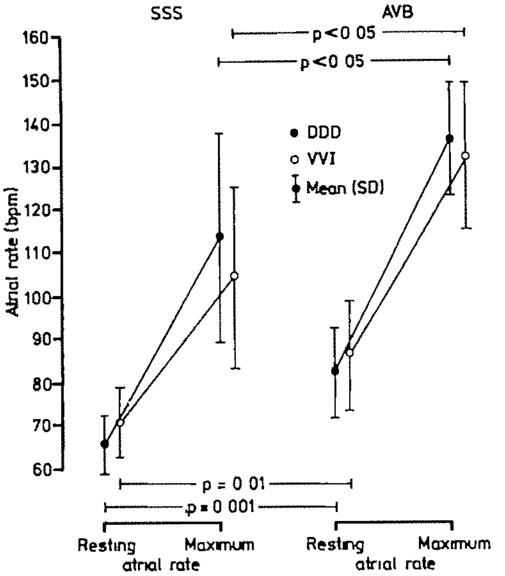

Fig 2 *Atrial rate at rest and during peak exercise in DDD and VVI modes in eight patients with sick sinus syndrome and eight patients with atrioventricular block.*

There were no significant differences in either the resting or maximum atrial rates achieved during the two pacing modes in the group with atrioventricular block (table 3). On the other hand, maximum atrial rates in the group with sick sinus syndrome were lower in VVI than in DDD mode (105 (22) *v* 114 (23) beats/min), but this difference was not statistically significant.

For both the DDD and VVI modes the atrial rates were significantly lower at rest in the sick sinus syndrome group than the atrioventricular block group (DDD: 66 (7) *v* 85 (10) beats/min (p = 0·001)); VVI: 72 (8) *v* 88 (14) beats/min (p = 0·01))

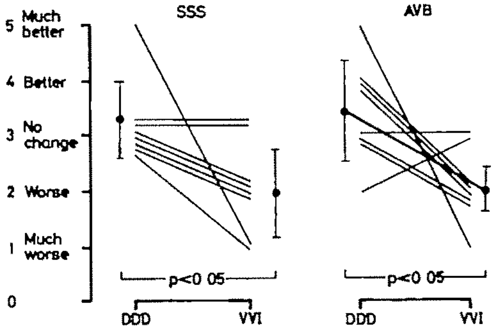

Fig 3 *Symptom scores for general wellbeing for DDD and VVI pacing modes in eight patients with sick sinus syndrome and eight with atrioventricular block.*

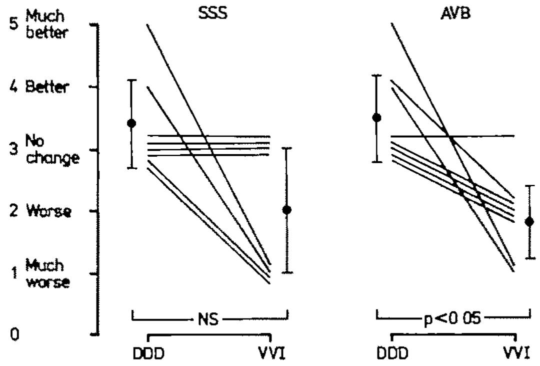

Fig 4 *Symptom scores for shortness of breath in DDD and VVI modes in eight patients with sick sinus syndrome and eight patients with atrioventricular block.*

(table 3 and fig 2). At peak exercise, the group with sick sinus syndrome again had significantly lower atrial rates than the group with atrioventricular block for both pacing modes—a difference of 20% in DDD and 23% in VVI mode (DDD 114 (23) *v* 138 (14) beats/min ($p < 0·05$)); VVI 105 (22) *v* 133 (17) beats/min ($p < 0·05$)).

DIARY CARDS

The subjective "feeling of general wellbeing" was significantly better in the DDD mode for both groups ($p < 0·05$) (table 3 and fig 3).

The subjective assessment of "shortness of breath" was also better for DDD pacing in atrioventricular block (3·5 (0·75) *v* 1·87 (0·84) ($p < 0·05$)) (table 3 and fig 4). In sick sinus syndrome, 50% of patients were more breathless in the VVI mode.

Table 4 compares the frequency of symptoms during VVI and DDD modes for both patient groups. No patient had syncopal episodes. Palpitation was more frequent during VVI pacing in patients with sick sinus syndrome ($p < 0·05$) for both the weekly attack rate and the monthly symptom score (fig 5). The frequency of palpitation for atrioventricular block patients was not different for the two pacing modes.

No patient with sick sinus syndrome complained of angina-like chest pain. In three of the eight patients with atrioventricular block angina-like chest pains were more frequent during DDD pacing. Patient 10 experienced no anginal episodes in VVI compared with several episodes in DDD mode and therefore preferred the VVI mode.

Fifty per cent of patients with sick sinus syndrome experienced dizziness more often during VVI pacing, but this difference did not reach statistical significance. Patients with conduction tissue disease experienced little dizziness in either pacing mode.

HOLTER MONITORING

During Holter monitoring in patients with sick sinus syndrome three cardiac arrhythmias were detected: short runs of atrial extrasystoles (3 to 5 consecutive beats), paroxysmal atrial fibrillation, and ventricular extrasystoles (both singles and pairs). In DDD mode, only one of the eight patients had paroxysmal atrial fibrillation and another showed 29 episodes of short

Table 4 *Weekly attack rates and monthly symptom scores of symptoms for individual patients*

Case No	*Palpitation (attacks/wk)* DDD	*Palpitation (attacks/wk)* VVI	*Dizziness (attacks/wk)* DDD	*Dizziness (attacks/wk)* VVI	*Chest pain (attacks/wk)* DDD	*Chest pain (attacks/wk)* VVI	*Symptom score "palpitation"* DDD	*Symptom score "palpitation"* VVI	*Symptom score "dizziness"* DDD	*Symptom score "dizziness"* VVI	*Symptom score "chest pain"* DDD	*Symptom score "chest pain"* VVI
Group 1 (SSS)												
1	0	0	0	0	0	0	3	3	3	3	3	3
2	0	0·6	1·25	1·75	0	0	4	2	4	2	3	3
3	0	0	0	1	0	0	3	3	4	2	3	3
4	0	0	0	0	0	0	3	3	3	3	3	3
5	0	1·75	0	1	1	1	3	2	3	2	3	3
6	0	2·5	0	0	0	0	3	2	3	3	3	3
7	1	27	0	0·25	4	6·5	5	1	3	2	3	2
8	0	13	3·5	1	0·5	2·5	5	1	3	3	4	2
Mean (SD)	0·12 (0·35)*	5·60 (9·68)*	0·59 (1·25)†	0·62 (0·65)†	0·68 (1·38)†	1·25 (2·29)†	3·6 (0·91)*	2·12 (0·83)*	3·25 (0·46)†	2·5 (0·53)†	3·12 (0·35)†	2·75 (0·46)†
Group 2 (AVB)												
9	0	0	0	1	0	0	3	3	4	2	3	3
10	0	0	0	0	3·25	0	3	3	4	2	1	5
11	0	10	0	0	0	8	3	1	3	3	3	1
12	0	0	0	0	0	0	3	3	3	3	3	3
13	0	1	0·25	2	0	0·5	3	2	3	2	3	3
14	1·25	0	0·5	0	13·5	2·25	2	4	3	3	2	5
15	3	2·75	0	0	3·25	2·75	3	3	3	3	3	4
16	0	0	0	0	0	0	3	3	3	3	3	3
Mean (SD)	0·53 (1·08)†	1·71 (3·48)†	0·15 (0·29)†	0·37 (0·74)†	2·5 (4·68)†	1·68 (2·77)†	2·87 (0·35)†	2·75 (0·88)†	3·12 (0·35)†	2·75 (0·46)†	2·62 (0·74)†	3·37 (1·30)†

*p < 0·05; †p = NS.

runs of atrial extrasystoles.

The frequency and duration of atrial arrhythmias were increased in VVI but the difference between the two modes was not statistically significant (fig 6).

In DDD mode, one of eight patients had frequent ventricular extrasystoles (>10/1000 beats). In VVI mode, two further patients had infrequent ventricular extrasystoles (<10/1000 beats; table 5).

In the DDD mode two of the eight patients developed runs of pacemaker mediated tachycardia that were brief, self-terminating, and asymptomatic.

In the DDD mode the mean heart rate was 64 beats/min and pacemaker use was 64%. In VVI mode the average heart rate was 74 beats/min and pacemaker use was 77% (NS). In both modes, as expected, the mean heart rate fell and pacemaker use increased at night (table 5).

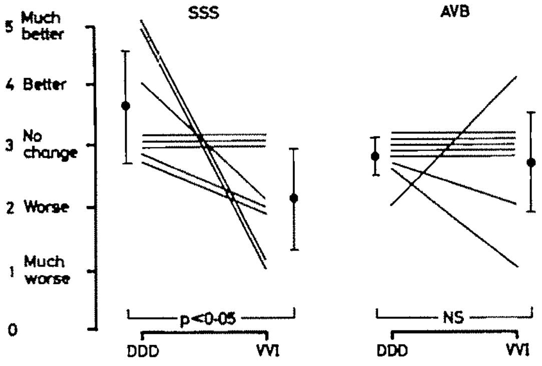

Fig 5 *Symptom scores in DDD and VVI modes for palpitation in eight patients with sick sinus syndrome and eight patients with atrioventricular block.*

Discussion

Because patients with sick sinus syndrome can develop sinus rhythm during exercise and thus were expected to show no difference in maximal effort tolerance between DDD and VVI modes we also studied symptom scores on diary cards and Holter monitoring in addition to exercise testing to assess pacemaker modes. Two exercise tests were performed before entry into the study to counteract the effect of training during subsequent exercise testing. This study was a within patient double blind trial. To eliminate bias both the patient and the investigators were blind to the randomly programmed pacing modes. None the less, some patients did recognise the change to VVI when their heart rate failed to increase with exertion or they developed symptoms. It is impossible for some patients to remain unaware of the pacemaker mode. One of us (SLC) testing was aware of the programmed mode during exercise and

Table 5 *Results of Holter monitoring in eight patients with sick sinus syndrome*

									Cardiac arrhythmias				
	Maximum atrial rate (beats/min)		*Mean heart rate (% of pacing rate)*						*Atrial arrhythmias (duration (min)*		*VE (no/1000)*		*PMT (duration beats)*
			Night		*Day*		*24 hour*						
Case No	*DDD*	*VVI*	*DDD*	*VVI*	*DDD*	*VVI*	*DDD*	*VVI*	*DDD*	*VVI*	*DDD*	*VVI*	*DDD*
Group 1 (SSS):													
1	86	118	64 (74)	72 (89)	66 (72)	76 (78)	65 (76)	75 (82)	0	PAF (76)	0	14	0
2	68	92	60 (96)	70 (100)	60 (75)	71 (93)	60 (88)	71 (93)	0	PAF (25)	0	2	0
3	93	96	60 (100)	70 (100)	69 (5)	71 (85)	68 (40)	73 (69)	PAF (110)	PAF (212)	0	0	0
4	84	80	60 (100)	70 (95)	60 (100)	70 (93)	60 (100)	70 (94)	0	0	0	0	1 (9)
5	74	72	—‡	70 (100)	64 (54)	71 (6)	61 (69)	71 (72)	0	0	0	14	5 (15–23)
6	76	70	60 (100)	70 (100)	61 (76)	70 (100)	60 (81)	70 (100)	0	0	11	0·5	0
7	102	100	60 (100)	70 (86)	75 (0)	73 (71)	69 (26)	71 (80)	AEs	0	0	0	0
8	114	152	61 (47)	71 (56)	70 (7)	95 (10)	66 (31)	87 (24)	0	0	0	1	0
Total									(110)	(313)			
Mean (SD) (%)	87 (15)	97 (27)	60 7 (1 5)* 88·1(20 5)	70 3 (7·4)* 90 6(15 1)	65 6 (5·4)† 48·6(39 0)	74 6 (8 4)† 67(37 6)	63·6 (3 8)* 63·8(27 8)	73·5 (5·7)* 76·7(23·9)			1 4 (3·9)	3 9 (6·2)	

*p < 0·01; †p < 0 05; no other comparisons were statistically significant.
‡Holter recording during this time was not satisfactory for analysis.
VE, ventricular extrasystoles; PMT, pacemaker mediated tachycardia; SSS, sick sinus syndrome; PAF, paroxysmal atrial fibrillation; AEs, short run of atrial extrasystoles.

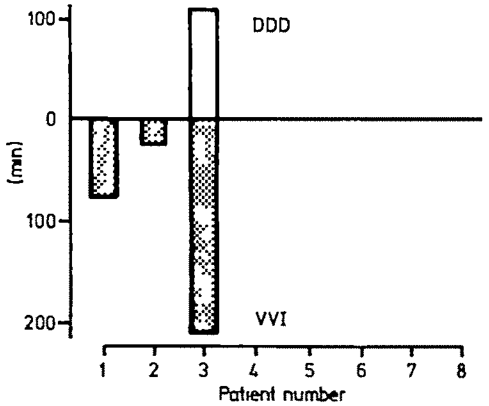

Fig 6 *Frequency and duration of atrial fibrillation in DDD and VVI pacing modes for each patient.*

monitored the electrocardiogram but took no part in the subsequent data analysis.

DIARY CARDS

This prospective controlled study showed that DDD pacing is better than VVI in patients with sick sinus syndrome, although there was no difference in effort tolerance between the modes and sinus rhythm developed on each occasion. The beneficial effects of the DDD mode in sick sinus syndrome were evident from the analysis of diary cards. Subjective symptoms of palpitation were significantly ($p<0·05$) less during DDD pacing; also the patient's overall feeling of wellbeing was significantly ($p<0·05$) improved. Shortness of breath, however, may be regarded as an exercise related symptom and DDD pacing was not better than VVI pacing in counteracting this symptom in the patients with sick sinus syndrome. In contrast, in patients with atrioventricular block DDD pacing had beneficial effects on both exercise tolerance and shortness of breath. Two patients were unable to tolerate VVI mode and required reprogramming to DDD before completion of the study period. One patient had sick sinus syndrome and the other had atrioventricular block. Both complained of palpitation, shortness of breath, and chest pain (non-anginal) which lasted for seconds to over an hour. These two patients had pacemaker syndrome in VVI.

This study design differed from that of Perrins *et al*[16] in that there was no randomised run-in period of one month before the trial itself began. All patients in both groups were in DDD before the trial. So after the first month the effects of the DDD mode could be compared with the DDD mode that was previously programmed in nine patients (four in group 1, and five in group 2). As expected, seven reported no change in shortness of breath but two reported an improvement. Both these patients also reported adverse effects when they changed to the VVI mode. Seven patients reported no change in wellbeing after the first month of study and two reported an improvement. Again both of them reported adverse effects in the second month when the VVI mode was operating. Only group 1 had a statistically significant difference between the modes for palpitation. None of the patients with no mode change in the first month reported a change but two of them reported an adverse effect when they changed to VVI in the second month of the trial. For shortness of breath in group 1 DDD was better than VVI in four, with no change in four; and for group 2 DDD was better in seven, with no change in one. For general wellbeing in group 1 DDD was better than VVI in four patients, with no change in four, and in group 2 DDD was preferred by eight with no change in one and VVI was favoured by one who had angina in the DDD mode. For palpitation five group 1 patients preferred DDD and three reported no difference. So only the patient who had angina in DDD preferred the VVI mode. These results indicate that the omission of the one month run-in period did not affect the comparison of the two pacemaker modes.

Pacemaker syndrome normally presents with symptoms of dizziness, syncope, chest pain, and shortness of breath. Several mechanisms have been proposed to explain this syndrome.[13 17] In the presence of retrograde atrioventricular conduction, left atrial pressure rises and cardiac output falls. This results in hypotension, which may be compounded by an inappropriate response in total peripheral resistance.[17–19] When retrograde atrioventricular conduction is not present, competition between sinus rhythm and ventricular pacing may induce hypotension by causing an acute and transient loss of atrioventricular sychrony.[20] In this study, most of the patients with sick sinus syndrome who completed the one month study period in VVI mode had symptoms and could be regarded as having a form of pacemaker syndrome (figs 3–5 and tables 3 and 4).

EXERCISE TESTING

Perrins *et al*[16] found that exercise tolerance and symptoms were better in patients with atrioventricular block in VDD (atrial triggered pacing) than in VVI pacing. In the VDD mode, if the atrial rate falls below the programmed low rate, the pacemaker functions as a VVI unit and this makes it unsuitable for pacing patients with sick sinus syndrome. In contrast, as the spontaneous rate decreases in DDD, the pacemaker paces sequentially in the atria and ventricles. In the present study symptomatic assessment of shortness of breath and general wellbeing in patients with atrioventricular block showed similar results to the study of Perrins *et al.*[16] But they found no difference in the frequency of chest pain between the VDD and VVI modes whereas two of our patients with atrioventricular block had frequent episodes of angina in the DDD mode. In VVI one patient had no angina and the other had an appreciable reduction in anginal episodes. These differences probably reflect differences in patient selection for these two small samples. Kristensson *et al* reported that a reduction in the upper rate in DDD improves the control of angina in patients with ischaemic heart disease.[21] Kenny *et al* confirmed this finding using a double blind technique.[22]

We compared the effect of the DDD mode in sex and age matched subjects with sick sinus syndrome and atrioventricular block. Effort tolerance was better in those with sick sinus syndrome than in those with atrioventricular block, but this difference was not statistically significant. It is possible that four of eight patients with atrioventricular block had ischaemic heart disease which may have limited their exercise tolerance without producing angina. Atrial rates at rest and at peak exercise were significantly lower in patients with sick sinus syndrome for both pacemaker modes. Holden *et al* also showed that there was no difference in effort tolerance in patients with sick sinus syndrome and normal age matched controls but atrial rates at peak exercise were lower in patients with sick sinus syndrome.[23] The maintenance of effort tolerance may be the result of haemodynamic adaptation to the relative sinus bradycardia in patients with sick sinus syndrome by augmentation of stroke volume[20] which suggests that in these patients maintenance of atrioventricular synchrony is more valuable haemodynamically than rate responsiveness on exercise.

It can be difficult to diagnose sick sinus syndrome in the presence of atrioventricular block. In the present study we assessed sinus node dysfunction in patients with atrioventricular block by routine electrocardiography, sinus node recovery times, and by Holter recordings. We found no abnormalities.

HOLTER MONITORING

Holter monitoring showed that the maximal sinus rates achieved on exercise testing are not seen in daily life and that patients spend much of their day with their hearts driven by their pacemakers. This accounts for the better symptomatic benefit shown by the diary cards for dual chamber pacing in terms of general wellbeing, dizziness, and palpitation.

In VVI mode, with a back up rate of 70 beats/min, patients used their pacemakers 77% of the time. Adverse symptoms in VVI mode are associated with retrograde atrioventricular conduction. It is of interest to note the degree of pacemaker use within a 24 hour period. Previous work showed that VVI pacing at 50 beats/min produces fewer adverse symptoms than rates of 70 beats/min.[24] This is directly related to the proportion of time that the heart is driven by the pacemaker. The DDD mode may have been better than the VVI mode in the present series because of the lower back up rate for DDD (60 *v* 70 beats/min). None the less, if retrograde atrioventricular conduction is present, VVI pacing will cause symptoms, whatever the pacing rate. In addition, if the back up rate is low, bradycardia may itself cause symptoms. The short runs of pacemaker mediated tachycardia in two patients were asymptomatic and such events can often be prevented by appropriate programming of the DDD mode.

This study shows that dual chamber pacing may be better than VVI in the prevention of paroxysmal atrial fibrillation (fig 6, table 5). Sick sinus syndrome is associated with a high incidence of both atrial fibrillation and systemic embolism,[25] which are likely to be related features.[26] The aim of atrial stimulation is to prevent bradycardia dependent atrial tachycardias and, by implication, systemic embolism. So far there is no convincing data to suggest that this has been achieved. Some workers, however, have shown a lower incidence of stroke, heart failure, and chronic atrial fibrillation when AAI pacing rather than VVI pacing is used[27 28] but no controlled studies have yet been reported.

Ours was a small short term study and other larger studies have been short term too, so we cannot be certain that suppression of atrial arrhythmias in sick sinus syndrome will persist. Atrial stimulation alone is unlikely to control all atrial arrhythmias, and some patients may also need antiarrhythmic drugs and even anticoagulants. DVI pacing improved symptoms in sick sinus syndrome more than VVI,[29] but Furman and Cooper suggest that the increased incidence of atrial arrhythmias in this dual chamber mode is presumably caused by its lack of an atrial demand feature.[9]

We found that DDD pacing was better than VVI pacing in patients with sick sinus syndrome, particularly those with retrograde atrioventricular conduction. Every sick sinus syndrome patient requiring cardiac stimulation should be considered as a candidate for dual chamber pacing. In this study we did not compare DDD with atrial demand pacing (AAI). However, a difference between AAI and DDD is unlikely in these patients who showed no evidence of atrioventricular block at pacemaker implantation. If DDD pacing is better than AAI we expect that it would appear by protecting against the development of atrioventricular block during the lifetime of the pacemaker which, with presently available dual chamber units, may be six years or more. There was progression to atrioventricular block causing clinical concern in 8·4% of patients with no initial atrioventricular conduction defect in a period of 34·2 months in a review of 1395 published cases.[8]

In the future it may prove valuable to use the DDI mode of pacing rather than DDD. In DDI both sets of chambers are paced on demand but atrial triggering of ventricular stimulation does not occur, which prevents the possibility of development of pacemaker mediated tachycardia and this avoids atrial tachycardias triggering a rapid ventricular rate, while DDI still provides all the other attributes of a DDD pacemaker. DDDR pacemakers are becoming available being equipped with an additional sensor to permit dual chamber rate responsive pacing (R) in the event of a lack of response to exercise by the atria. These pacemakers need careful evaluation both in terms of control of symptoms and of atrial arrhythmias and their suppression.

We thank Rosalind Wood for statistical assistance.

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Case reports

Coronary venous aneurysms and accessory atrioventricular connections

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SUMMARY Histological investigation of a heart with aneurysmal malformation of the anterior cardiac vein showed atypical accessory atrioventricular pathways that could have been the basis for bypass tracts and ventricular pre-excitation. Review of other cases with coronary sinus or venous aneurysms showed a striking association with sudden death. Such malformations may not be as benign as previously thought.

Aneurysmal malformations of the coronary sinus and coronary veins are not often reported. When present they are casual findings and thought to be of little clinical importance[1] except in association with ventricular pre-excitation.[2] We describe a further case with this malformation, which prompted us to re-examine a previous case.

Case report

The patient, a girl born at Southmead Hospital, presented with a neonatal arrhythmia. The electrocardiogram showed a tachycardia of 200 beats per minute with wide QRS complexes and without obvious P waves. This was interpreted as showing an antidromic tachycardia in association with the Wolff-Parkinson-White syndrome (fig 1). Cardiac catheterisation was performed when she was 11 weeks old. This showed an oval fossa defect with a large right atrium. A curved, band-like chamber below the lower margin of the right atrium was interpreted as being the coronary sinus. The patient suffered a cardiac arrest during this procedure but resuscitation was successful. The parents refused any further investigation. Subsequent medical history was not available. The child died suddenly at the age of 12.

Necropsy findings limited to the heart showed an enlarged heart weighing 243 g which had the usual chamber connections and relations with intact septal structures. An aberrant chamber composed of several

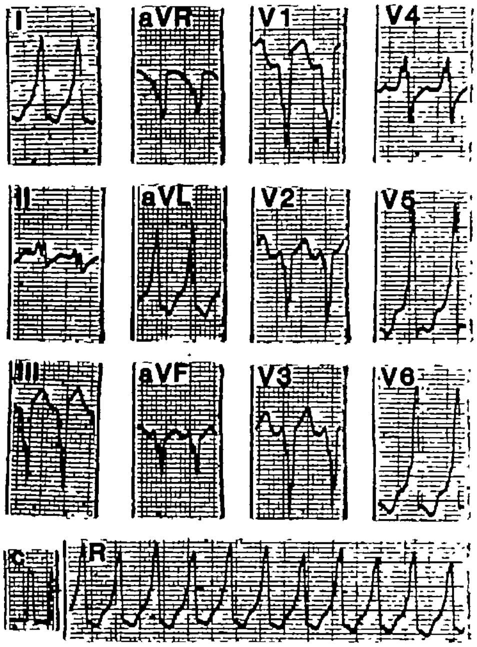

Fig 1 *Standard lead electrocardiogram. c, calibration 1 mV; R, rhythm strip.*

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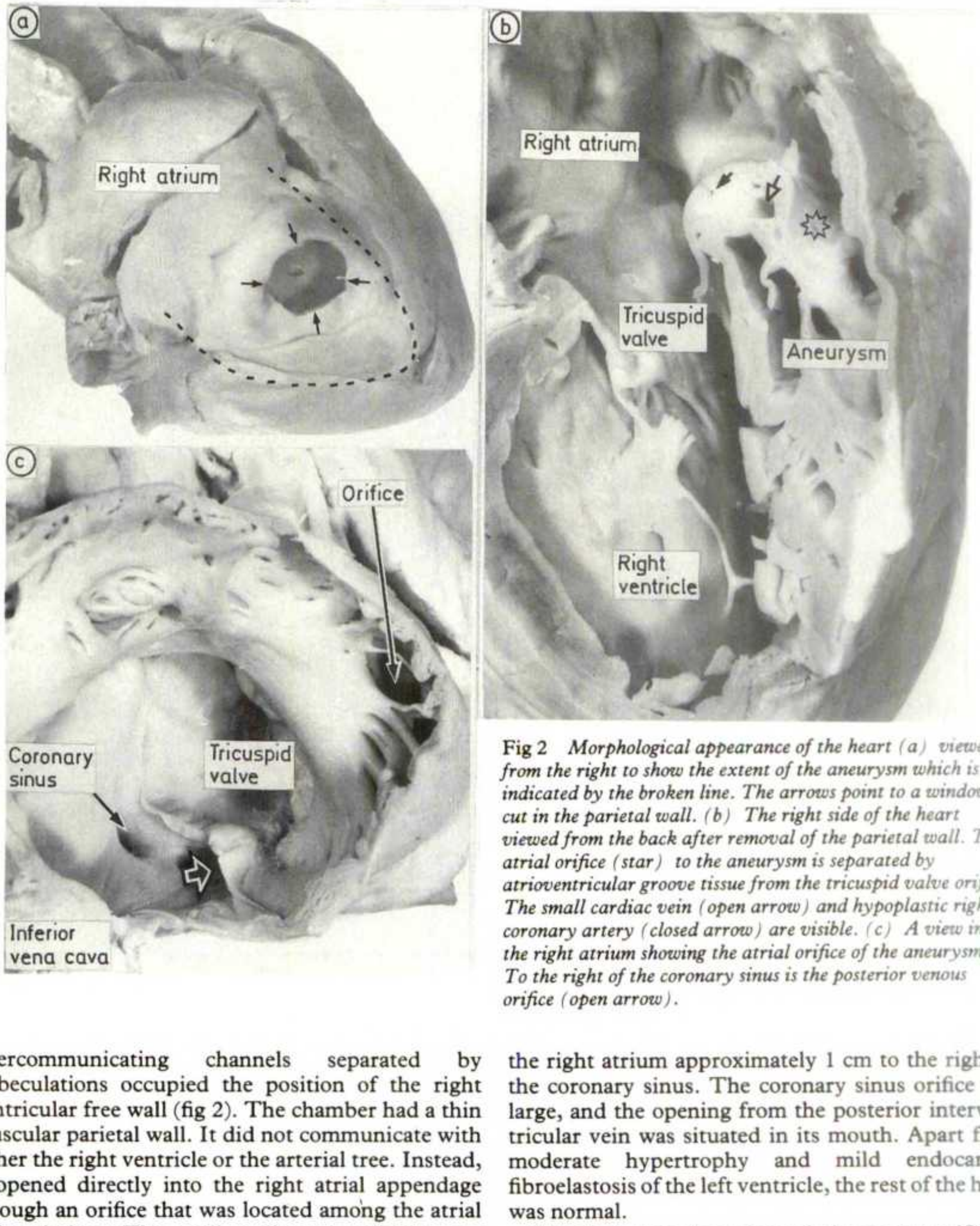

Fig 2 *Morphological appearance of the heart (a) viewed from the right to show the extent of the aneurysm which is indicated by the broken line. The arrows point to a window cut in the parietal wall. (b) The right side of the heart viewed from the back after removal of the parietal wall. The atrial orifice (star) to the aneurysm is separated by atrioventricular groove tissue from the tricuspid valve orifice. The small cardiac vein (open arrow) and hypoplastic right coronary artery (closed arrow) are visible. (c) A view into the right atrium showing the atrial orifice of the aneurysm. To the right of the coronary sinus is the posterior venous orifice (open arrow).*

intercommunicating channels separated by trabeculations occupied the position of the right ventricular free wall (fig 2). The chamber had a thin muscular parietal wall. It did not communicate with either the right ventricle or the arterial tree. Instead, it opened directly into the right atrial appendage through an orifice that was located among the atrial trabeculations. The small cardiac vein, which was a continuation of the infundibular vein, ran within atrioventricular groove tissue close to the tricuspid valve. A hypoplastic right coronary artery was present within groove tissue. The aberrant chamber connected with the small cardiac vein anteriorly and became confluent posteriorly just distal to the acute margin. The combined venous orifice opened into the right atrium approximately 1 cm to the right of the coronary sinus. The coronary sinus orifice was large, and the opening from the posterior interventricular vein was situated in its mouth. Apart from moderate hypertrophy and mild endocardial fibroelastosis of the left ventricle, the rest of the heart was normal.

Histological sections through the venous orifice in the right atrial appendage showed continuity between atrial and ventricular myocardium (fig 3). A 2 mm wide band of enlarged and aligned myocytes passed from the component of atrial wall which formed the parietal aspect of the orifice into the parietal wall of the aneurysm. There was a second band of myocardial continuity to the medial side of

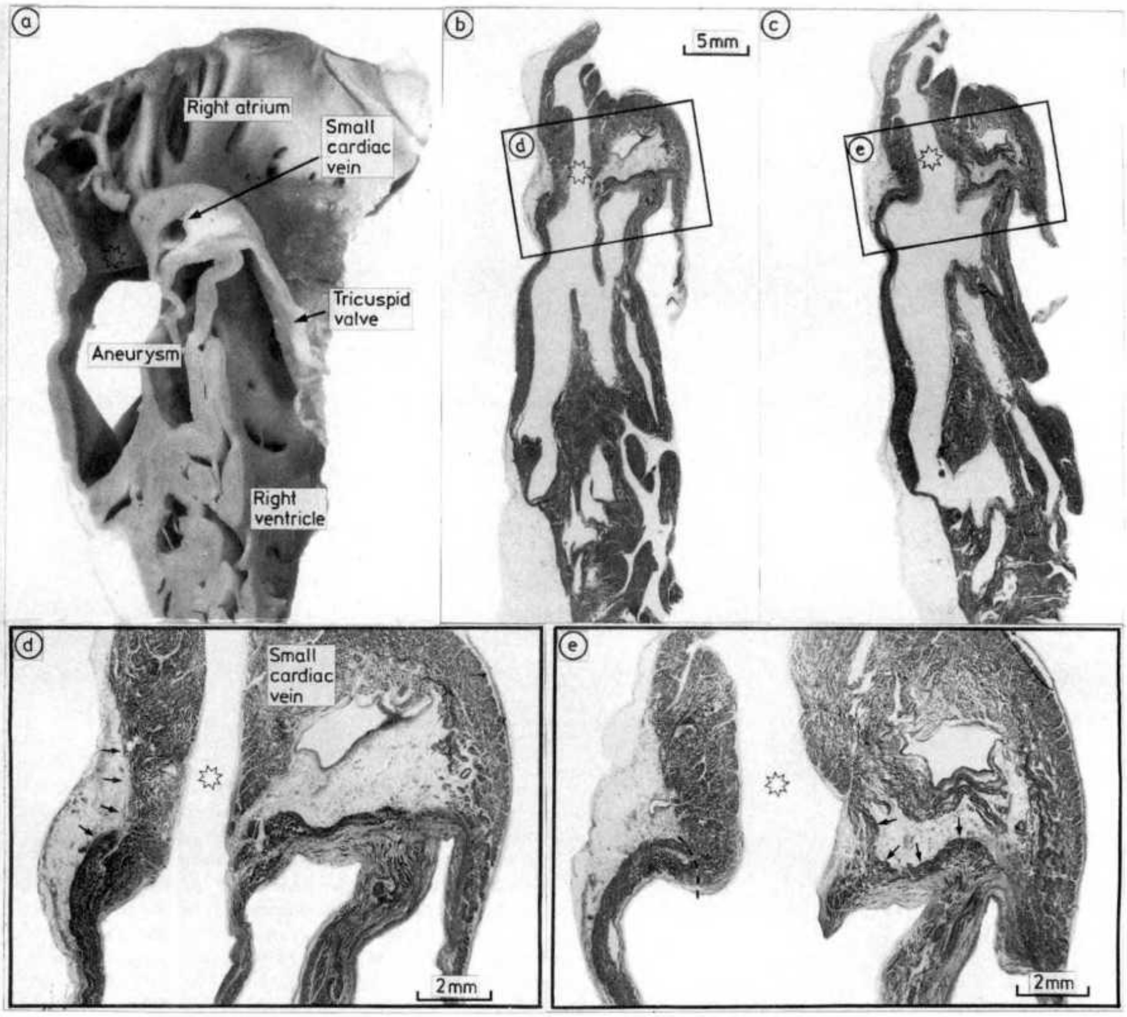

Fig 3 *The tissue block removed for histological study is shown in (a). Step sections (b and c) with enlargements of the respective boxed areas in (d) and (e). The orifice of the aneurysm is marked by the star in each panel. The accessory connections are indicated by the series of arrows in (d) and (e). Although the parietal wall in (e) shows apparent muscular continuity, there is actually fibrous separation in the area marked by the broken line.*

the orifice that ran between the orifice and the small cardiac vein (fig 3) before connecting with the party wall between aneurysm and right ventricle.

Discussion

There are few published reports on the embryogenesis of the human cardiac vein. Studies on the rabbit heart showed that the cardiac veins appeared before the arteries.[3] The main venous system started as endothelial buds from the coronary sinus. Other outgrowths also developed from the atria and the ventricles. Those from the right atrium may retain their atrial connections to form the anterior cardiac veins or anastomose with the main venous system to open into the coronary sinus. In early development, the atrial and ventricular myocardium is continuous.[4] Continuity around the atrioventricular junction is interrupted by an ingrowth of atrioventricular groove tissue.[5] In normal circumstances, muscular continuity is preserved only at the atrioventricular conduction bundle. Persistence of other myocardial bridges provides the potential for ventricular pre-excitation through accessory atrioventricular connections.[6]

Most accessory atrioventricular connections are related to the annular insertions of the atrioventricular valves in the parietal and septal regions.[7] Infrequently, histological confirmation of atrioventricular connections is found remote from the valve insertions.[2] Our case is another instance in which myocardial continuity was provided by extensive bands that formed the subepicardial and medial walls of the venous aneurysm. There was inadequate myocardial retrogression[4] and lack of sequestration by groove tissue in the region of the anterior atrial venous openings. The myocardial bands may be interpreted as persistence of the primitive atrioventricular myocardial connection carried by outgrowing endothelial buds from the right atrium, while the aneurysm is a malformation of the anterior cardiac veins.

The three previous reported patients with venous aneurysms or aneurysms of the coronary sinus died suddenly.[1 2] In two of these, there was electrocardiographic evidence of Wolff-Parkinson-White syndrome together with histological demonstration of the accessory pathways. We have reviewed the heart of case 2 that we reported on earlier[1] (in which there was no evidence of Wolff-Parkinson-White syndrome) and we found potential muscular continuity between atrial and ventricular myocardium through the outer wall of the coronary sinus aneurysm. We believe that this could form the basis for a bypass tract. In view of the alarming association of sudden death with coronary sinus or venous aneurysms, we believe that such malformations may not be as benign as was previously thought. The potential for subepicardial myocardial bridges is enormous because of extensive conjugation between atrial and ventricular myocardium through the outer wall of the aneurysm. These bridges are atypical accessory connections but in our opinion they are easier to ablate than the regular annular types. In our present case both the parietal and medial bands may have been amenable to ablation by cryothermy or dissection around the mouth of the venous aneurysm.

The pattern of pre-excitation seen on the electrocardiogram in this case is consistent with a right sided accessory pathway[8 9] which could have been either anterior or posterior. It is possible that, with more extensive sectioning, further accessory connections would have been found. Although it is not possible to be precise about the arrhythmia, it is reasonable to assume that sudden death was caused by atrial fibrillation in Wolff-Parkinson-White syndrome. Because none of the cases with atypical pathways were investigated electrophysiologially, it is not possible to comment on whether the refractory characteristics of the subepicardial pathways were different from pathways that were more adjacent to the cardiac cavities.

We thank Dr S Jordan for the clinical information on this case and Dr L Gerlis for his encouragement throughout this investigation and for preparing fig 1, and Professor R Anderson for his helpful advice.

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Type A Wolff-Parkinson-White syndrome obscured by left bundle branch block associated with a vascular malformation of the coronary sinus

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SUMMARY A case of Wolff-Parkinson-White syndrome type A with coexisting ipsilateral bundle branch block is presented. The diagnosis was suspected because of subtle electrocardiographic changes and was confirmed at electrophysiological study. Necropsy showed a vascular anomaly of the coronary sinus that contained bundles of myocardial muscle which crossed the atrioventricular ring at a site that was consistent with the predicted accessory pathway.

In the Wolff-Parkinson-White syndrome the diagnosis of coexisting bundle branch block may be obscured by the presence of an accessory pathway on the same side of the heart.[1] We report a case of Wolff-Parkinson-White syndrome in which a left sided accessory pathway was confirmed at necropsy in a patient known to have left bundle branch block.

Case report

A 66 year old woman was studied because she had recurrent episodes of paroxysmal supraventricular tachycardia that were resistant to conventional medical management because of coexistent sinus node disease.[2] A dual demand pacemaker designed to switch into a fixed rate mode at 70 beats/min when the heart rate exceeded 150 was successfully implanted and controlled the arrhythmia. The electrocardiographic and electrophysiological studies were reported in detail elsewhere.[2-4]

The resting electrocardiograms at the time of presentation had shown the appearance in fig 1a and she was referred with the diagnosis of Wolff-Parkinson-White syndrome type B. The configuration of left bundle branch block was seen in escape complexes[5] (fig 1b) and during orthodromic tachycardia (fig 1c); the features of the Wolff-Parkinson-White syndrome type A were seen on one occasion, immediately after conversion to sinus rhythm by intravenous verapamil (fig 1d).

At electrophysiological study orthodromic reciprocating atrioventricular tachycardia with left bundle branch block configuration was initiated by premature right atrial extrastimuli. The earliest retrograde activation was seen in the left pulmonary artery indicating the presence of a left sided accessory atrioventricular pathway. Sinus node recovery was prolonged and episodes of tachycardia were frequently initiated by His escapes after sinus pauses.[2] A

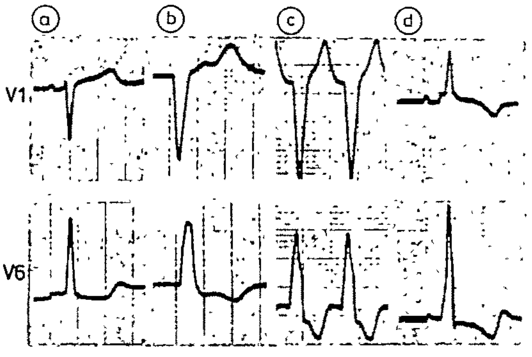

Fig 1 *Electrocardiograms (V1 and V6) showing (a) sinus rhythm, (b) junctional escape beats with left bundle branch block, (c) paroxysmal tachycardia (orthodromic) with left bundle branch block, and (d) sinus rhythm with positive delta waves and tall R waves in both leads after termination of tachycardia with verapamil. (Reproduced with permission from Krikler et al[4].)*

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mercury-zinc pulse generator was replaced after two years by one that used a lithium iodide battery; this continued to function until her death 11 years later.

At the age of 79 she complained of recurrent palpitation which was controlled by amiodarone. Several months later she was admitted to another hospital with acute chest pain; myocardial infarction was suspected and she died suddenly.

Necropsy showed acute anteroseptal myocardial infarction with diffuse atherosclerosis causing considerable stenoses of all three major coronary arteries; the heart had already been dissected by the coroner's pathologist. A vascular abnormality (fig 2), consisting of a mass of large dilated veins, was found on the posterior wall of the left ventricle. It drained directly into the coronary sinus. The muscle bundles around these vessels crossed the atrioventricular ring. At the apex of the muscular interventricular septum there was pronounced sclerotic fibrosis associated with total loss of the proximal portion of the left bundle branch and severe loss of conduction fibres in the adjacent bifurcating atrioventricular bundle. Elsewhere the muscular interventricular septum showed old ischaemic scarring. The morbid anatomical changes were those of bundle branch fibrosis as described by Lev.[5] The sinoatrial node showed almost total non-specific loss of specialised myocytes with a normal nodal artery.

The electrocardiograms at the time of her final admission were incomplete and no conclusions could be drawn about the effect of the acute ischaemic episode on the patterns of the pre-existing conduction abnormalities.

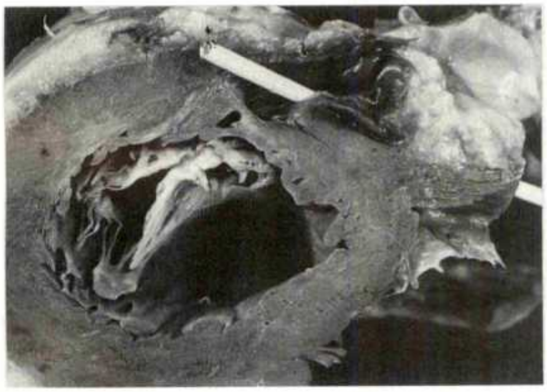

Fig 2 *Short axis view of the left ventricle at the level of the mitral valve. The probe is in the coronary sinus and enters a large vascular anomaly behind the left ventricle.*

Discussion

Although there are several reports of the coexistence of left bundle branch block with a left sided accessory pathway,[1 6] anatomical confirmation has been lacking. To our knowledge this is the only report of coexisting Wolff-Parkinson-White syndrome and ipsilateral bundle branch block that was suspected on the electrocardiogram, diagnosed at electrophysiological study, and confirmed anatomically.

Because of the coexisting sinus node disease and the complex pattern of pre-excitation a dual demand pacemaker was implanted. This lasted well and required only one change of pulse generator.

In the last year of her life, however, she complained of more frequent episodes of tachycardia, during which the pacemaker did not respond appropriately. This was related to spontaneous prolongation of the arrhythmia cycle length by about 70 ms resulting in a tachycardia rate of 125/min that failed to trigger the fixed rate mode and thus terminate the arrhythmia.

During the original electrophysiological study the left bundle branch block could be dissipated by a stimulus strong enough to enter the distal left bundle, implying a discrete, rather than a diffuse, lesion of that branch of the conducting system.[2] This prediction was confirmed at necropsy. When the accessory pathway is found on the same side as the bundle branch block the absence of the pattern of the bundle branch block suggests that discrete interruptions, rather than diffuse disease, may be most often responsible for disturbances of the conduction system in patients with the pre-excitation syndrome.

The vascular lesion present near the coronary sinus contained muscle fibres in the subpericardial wall, which formed the accessory connection between atrium and ventricle. Detailed anatomical studies of the Wolff-Parkinson-White syndrome are still rare but there is a report of a vascular anomaly of the cardiac venous system that drains into the coronary sinus.[7] This established an anomalous connection because it contained an outer layer of myocardial tissue that crossed the atrioventricular ring.[7] Surgeons too have reported finding such abnormalities during the course of division of accessory pathways,[8] and because of the complications they can cause the possibility that they are present should always be borne in mind whenever an operation or endocavitary ablation is planned.

This unusual type of accessory atrioventricular connection could not be inferred from the clinical and electrocardiographic features. The present patient did, however, illustrate the value of careful analysis of the electrocardiogram in predicting complex lesions that were corroborated by electrophysiological studies and confirmed at necropsy.

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Br Heart J 1988;60:355–7

Periarterial abscess: another cause of cyanosis after pulmonary artery banding

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SUMMARY Twenty seven months after pulmonary artery banding a boy aged two and a half developed rapidly progressive cyanosis. A periarterial abscess was found at the site of the band. Repair of the pulmonary artery and closure of the ventricular septal defect were complicated by profoundly low cardiac output and prolonged dependence on a ventilator. This near fatal complication would have been avoided by primary closure of the ventricular septal defect.

Constriction of the pulmonary artery to reduce pulmonary blood flow in the presence of an isolated ventricular septal defect is usually well tolerated and rapidly controls congestive heart failure. Although ventricular hypertension leads to progressive hypertrophy of the right heart, patients generally grow well and are usually symptom free for several years after a satisfactory banding operation.[1 2] The gradual appearance of cyanosis indicates the reversal of the intracardiac shunt, as the resistance in the enlarging systemic circulation progressively falls below that offered by the fixed diameter of the main pulmonary artery. A sudden onset or rapid progression of cyanosis, however, is more ominous, and in the patient presented here resulted from a serious and previously unreported complication of pulmonary artery banding.

Case report

A boy with Down's syndrome, who weighed 11 kg, was referred with increasing cyanosis and breathlessness at the age of two and a half. He had had severe congestive heart failure with failure to thrive in infancy, and cardiac catheterisation showed systemic pressure in the pulmonary artery with a large left to right shunt through a perimembranous ventricular septal defect. Pulmonary artery banding had been performed, without complication, at the referring institution when he was four months old, and he subsequently made satisfactory progress. Two months before admission, his mother noted slight central cyanosis, and five weeks later his condition rapidly deteriorated.

On examination, the boy was deeply cyanosed, lethargic, and tachypnoeic at rest. A grade 3/6 systolic murmur radiated from the left sternal border to the pulmonary area, but a thrill was not palpable. His chest was clear, but there was severe finger clubbing. The remainder of his examination showed findings that are typical of Down's syndrome but no other significant abnormality.

A chest *x* ray showed severely oligaemic lung fields and moderate cardiac enlargement, while the electrocardiogram showed right ventricular hypertrophy. Real time echocardiography showed a large ventricular septal defect and good ventricular function. On Doppler examination, a velocity of 4 m/s across the band suggested a gradient of 64 mm Hg. At cardiac catheterisation, pressure in the right ventricle was suprasystemic, and oxygen saturation in the aorta was 28% (table). Angiography confirmed the presence of a perimembranous ventricular septal defect, a tight pulmonary artery band, and a main

Table *Data from cardiac catheterisation*

	Pressures (mm Hg)	*Oxygen saturation (%)*
RA	7	26
RV	115/10	26
PA*	80/0	—
LV	95/5	40
Aorta	90/45	28

*Proximal to the band.
RA, right atrium; RV, right ventricle; LV, left ventricle; PA, pulmonary artery.
Pressures are given as systolic/diastolic for the RV, PA, LV, and aorta and mean for the RA.

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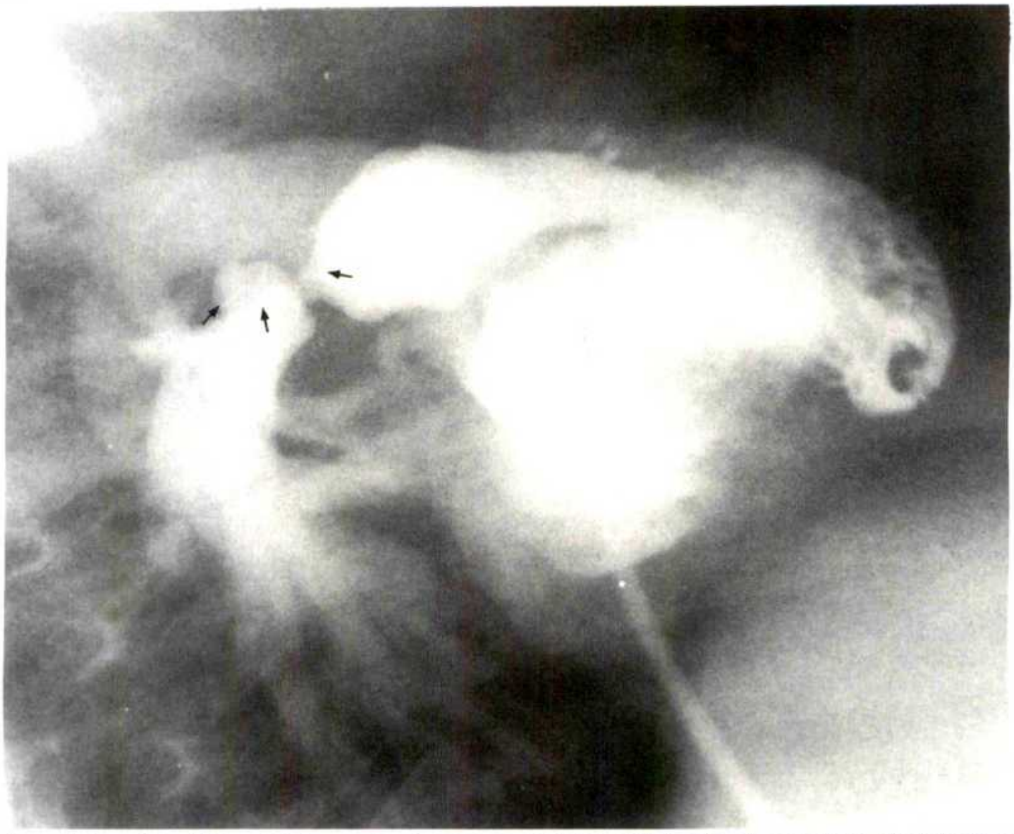

Fig *Lateral view of the right ventriculogram showing severe constriction at the banding site and the profile of the abscess mass (arrows).*

pulmonary artery with a long, irregular profile (figure).

In view of the probable thrombotic obstruction of the pulmonary artery, urgent debanding and closure of the ventricular septal defect were carried out on cardiopulmonary bypass. The pericardial space was obliterated by friable vascular adhesions, which suggested an active inflammatory process, and on palpation the position of the band was ill-defined as the result of dense fibrous tissue overlying the pulmonary artery. An incision into this mass entered a large abscess cavity containing thick, yellow pus under tension. The arterial endothelium was intact but a considerable portion of the main pulmonary artery had been destroyed by infection, and a silk ligature that had been used to band the pulmonary artery restricted the diameter of the lumen to about 3 mm at the bottom of the abscess cavity.

After evacuation of the abscess cavity, the pulmonary artery was reconstructed by end to end anastomosis posteriorly and a patch of autogenous pericardium anteriorly. The large, perimembranous ventricular defect was closed with a Dacron patch. Despite an initial pressure ratio of 0·53 between right and left ventricles, the patient had severe low cardiac output, which failed to respond to dopamine, isoprenaline, and adrenaline, in the immediate postoperative period. Chest *x* rays showed pulmonary oedema and subsequently collapse of the right upper lobe. Haemodynamic function gradually improved on the second postoperative day, but five days of mechanical ventilation and inotropic support were required before his condition stabilised. The remainder of his three week convalescence in hospital was uneventful. Pus from the abscess cavity was sterile.

Discussion

Before surgical correction of cardiac defects was feasible in infancy, pulmonary artery banding was used to palliate various malformations associated with excessive pulmonary blood flow.[2] Progressive, dense fibrosis of the arterial wall was seen as early as 14 weeks after pulmonary artery banding,[3 4] and similar thickening was found in the pulmonary valve itself.[1,4,5] Distal migration of the band[1,3] may cause preferential constriction of the right pulmonary artery and complicate debanding,[4] while erosion into the lumen of the pulmonary artery[6,7] occasionally produces cataclysmic haemorrhage. Calcification of the proximal pulmonary artery and the band site itself[8] and septic ulceration resulting in rupture of the vessel[7] are rare events. About 10% of patients in whom the pulmonary artery is banded will develop obstruction of the left ventricular outflow tract,[9] and obstructive right ventricular hypertrophy has been reported.[1,4]

The only other patient in whom a sudden and rapid deterioration with progressive cyanosis and clubbing was reported was found to have thrombosis of the pulmonary artery and died in severe low cardiac output six hours after operation.[10] In our patient, it seems clear that the expanding abscess compressed the pulmonary artery and produced a critical reduction in pulmonary blood flow. Though it is difficult to account for the lack of fever or other signs of infection, this may have been the result of the impaired immune system associated with Down's syndrome.[11] Certainly, the patient's rapid clinical deterioration over a period of a few weeks contrasts sharply with gradual development of cyanosis that occurs as the band is "out-grown". Such deterioration should prompt urgent reinvestigation because it suggests occlusion of the main pulmonary artery. Given the present excellent results of primary closure of the ventricular septal defect in infancy[12] and this near fatal complication of palliative surgery, there seems to be little justification in contining to perform pulmonary artery banding in patients with isolated ventricular septal defect.

We thank Dr Raman Patel and Dr Robert Arnold for permission to report this case. PLB was supported by the National Heart Research Fund.

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Br Heart J 1988;**60**:358–60

Balloon closure of a surgical aorto-atrial communication

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SUMMARY Surgical repair of an extensive dissection of the proximal aorta (Shumway type A or DeBakey type I) was complicated by persistent haemorrhage from the surgical suture lines and via the false lumen. This was controlled by closing the aortic adventitia round the repaired aorta and by creating an anastomosis between the subadventitial space and the right atrial appendage. Though the haemorrhage was contained, the left to right (aorto-atrial) shunt led to a severe low output state, which was corrected by percutaneous closure of the fistula with a detachable balloon. A year after operation computed axial tomographic scanning showed the balloon in place though the para-aortic space persisted and communicated freely with the aorta.

Case report

A 72 year old woman was referred from another London centre. Two days before she had been admitted with a seven hour episode of severe retrosternal chest pain that culminated in collapse. There was a history of treated hypertension, cigarette smoking, and airways obstruction. She was in pain and drowsy with a systolic blood pressure of 80 mm Hg. Heart sounds were soft and pulses were normal. The initial chest radiograph showed mediastinal widening and a left pleural effusion. Serial electrocardiograms showed inverted T waves and ST segment depression in the anterolateral leads. The concentration of blood urea was 8·7 mmol/l, serum creatinine was 75 μmol/l, haemoglobin was 10·4 g/dl, and the cell white count was $9{\cdot}2 \times 10^9$/l. A computed tomographic scan showed a Shumway type A dissection of the aorta extending from the annulus of the aortic valve to the descending thoracic aorta, with a small pericardial effusion.

Because of a rapid rise in blood pressure she was treated with hypotensive agents but the aorta continued to widen. Radiographic contrast aortography showed a type A dissection of the aorta with an intimal tear approximately 4 cm above the aortic annulus, a competent aortic valve, and mid-course occlusion of a non-dominant right coronary artery. Because of these findings an operation was performed.[1 2]

At operation, the arterial pressure was controlled with nitroprusside and the left atrial pressure was monitored indirectly. An atriofemoral bypass was established, the patient was cooled to 18 C, and thiopentone (2 g) was administered for cerebral protection. Total circulatory arrest lasted 35 minutes. When the aortic dissection sac, which affected the entire thoracic aorta, was incised an unusual longitudinal intimal entry tear was identified quite high in the ascending aorta. The ascending aorta was replaced with 24 mm Meadox hemishield, and the repair was wrapped in adventitia.[2] The aorta distal to the repair continued to distend and a further large intimal tear in the arch slightly distal to the left subclavian origin (the probable reentry site) was located and treated by the insertion of buttressed sutures. Despite these measures profuse haemorrhage continued via the adventitia enclosing the ascending aorta. This was consistent with one or more defects of the suture line, and a fatal outcome seemed probable. As a lifesaving measure, the haemorrhage was controlled by fashioning a communication between the subadventitial space and the right atrial appendage; this decompressed the para-aortic lumen by allowing blood to return to the venous circuit. Without this manoeuvre there was no prospect of weaning the patient off bypass. After construction of the anastomosis, bypass was stopped without difficulty.

Hopes that shunting from the aorta would decline because of thrombus formation in the para-aortic space were not realised. Progress over the next 48 hours was satisfactory, but thereafter the left to right

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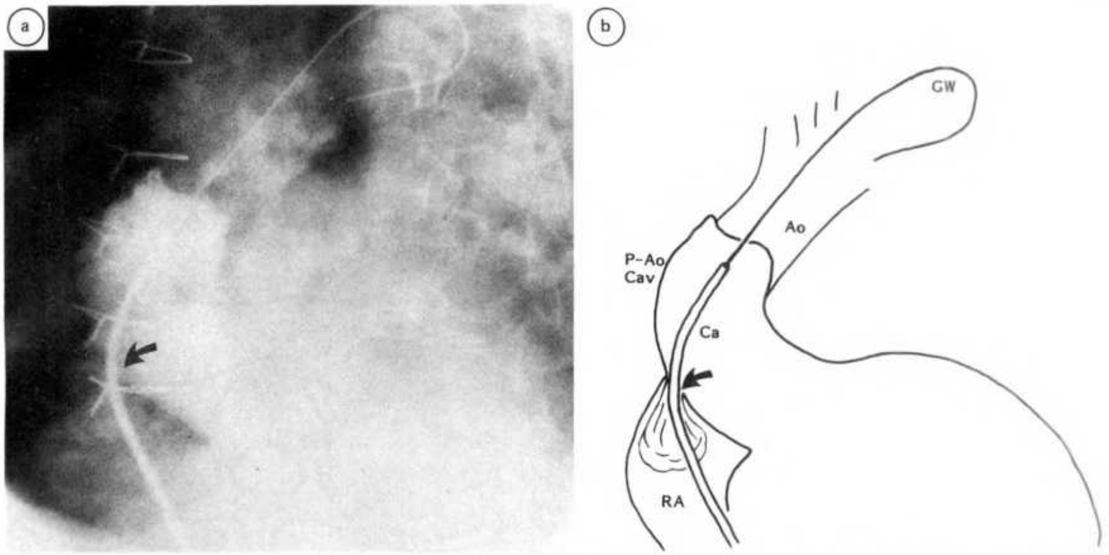

Fig 1 *A single frame (left anterior oblique view) from a cineaortogram exposed during positioning of 0·38 gauge guide wire (GW) and 8·8 French gauge introducing catheter (Ca) across the aorto-atrial fistula during placement of the Debrun apparatus. Contrast was injected via the introducing catheter into the para-aortic cavity (P-Ao Cav) close to the fistula (arrow), and is seen jetting into the right atrial appendage (RA). The guide wire lies in a cephalad region of the para-aortic space into which contrast has not penetrated. Contrast is principally confined to the vicinity of the prosthetic aortic replacement. Ao, aortic lumen.*

(aorto-atrial) shunt became increasingly active, leading to an intractable low output state and oliguric renal failure (peak blood urea 30·5 mmol/l and serum creatinine 218 μmol/l). So five weeks after the operation we used a percutaneous balloon technique to close the defect.

The right femoral vein was cannulated and a 7 French gauge Gensini catheter (Cordis UK Ltd) with a 0·38 gauge 145 cm long guide wire with a flexible tip (Cook UK Ltd) was advanced from the right atrium through the fistula into the para-aortic false lumen. We used a 260 cm exchange wire (Cook UK Ltd) to replace the Gensini catheter with an 8·8 French gauge 100 cm polyethylene catheter (Becton Dickinson, New Jersey, USA) (fig 1). Through this we sited a 2·2 ml capacity Debrun detachable balloon assembly (Ingenor Medical Systems, France (from Kimal, UK)) in the false lumen. The assembly was made up of a 2 French gauge single lumen catheter with a latex balloon attached to its tip by latex thread before use and an outer 3 French gauge coaxial catheter. The balloon was manoeuvred within the false lumen to lie close to the atrial communication. Test inflations with contrast medium (Conray 280) established how much the balloon needed to be distended to ensure that it became lodged against the fistula and prevented repassage into the right atrium. When the best site for the balloon had been established, it was drained of contrast material and refilled with the correct volume of silicone solution mixed with a chemical activator that solidified in about 20 minutes after mixing. The setting time within the balloon was determined by testing a small quantity of the mixture in a container. After the mixture had solidified the 3 French gauge outer catheter was advanced over the inner catheter to detach the balloon, which was left in position against the fistula. The introducing assembly was then withdrawn.

Before placement of the balloon the oxygen saturation of blood in both the superior and inferior venae cavae was 48% and that in the right atrium was 62%. These values were unchanged immediately after the procedure, though the right atrial pressure decreased from a mean of 16 mm Hg to 12 mm Hg. During the next 10 days, however, right ventricular overactivity decreased, heart failure cleared, and renal function returned to normal (blood urea 3·0 mmol/l and serum creatinine 61 μmol/l). The patient did not agree to have further elective contrast aortography and was discharged well nine weeks after operation.

A year after operation, the aorta had not expanded further and the shunt was undetectable by clinical criteria. A computed axial tomographic scan with contrast (fig 2), however, showed that the para-aortic lumen remained open and was connected with the true lumen while the communication to the right atrium was plugged by the Debrun balloon. The patient, now aged 73, has sustained two minor

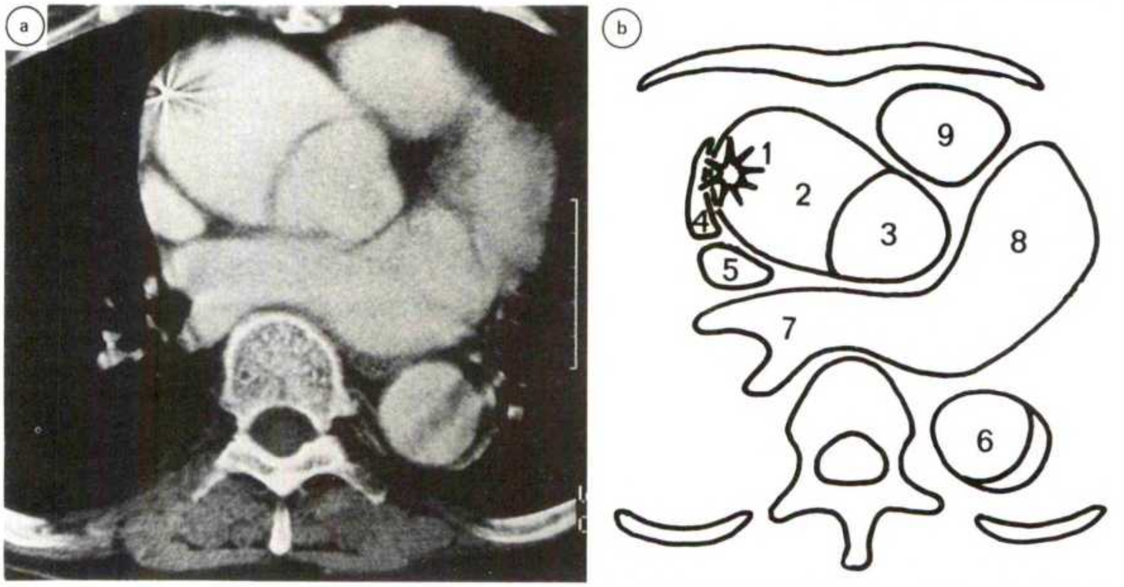

Fig 2 *Computed axial tomographic scan with intravascular contrast, obtained one year after operation. Transverse cut at the level of the ninth thoracic vertebra showing the "starburst" effect created by the silver clip within the Debrun balloon* (1)*, sited on the aortic aspect of the occluded aorto-atrial communication.* (2) *Para-aortic cavity enclosing dissected ascending aorta;* (3) *true lumen of ascending aorta;* (4) *right atrial appendage;* (5) *superior vena cava;* (6) *descending aorta (also dissected);* (7) *pulmonary veins entering left atrium;* (8) *left ventricle;* (9) *right ventricular outflow tract.*

cerebrovascular accidents, and is slightly disabled. No further intervention is planned.

Discussion

This patient needed an operation to stop the expansion of a type A dissection of the aorta.[1,2] We hoped that the communication that we created to deal with life threatening haemorrhage at operation would close spontaneously, but flow through the shunt progressed to imperil survival and make a further operation too hazardous. At first the balloon did not completely obstruct the aorto-atrial shunting, but subsequently the latex surface induced formation of thrombus, which produced more complete closure. Also the balloon may have impacted more fully with time. The Debrun apparatus is designed primarily to close fistulas and aneurysms of the large cerebral arteries.[3] These carry high flows and are not end arteries. The risk of embolism of the occluding device is high in an aortic dissection and so it must be carefully positioned. The siting of the balloon is precise and potentially reversible until the final stage, unless gelfoam or steel coils are used. Detachable balloons have been used to close Blalock-Taussig shunts and congenital coronary arterioarterial and coronary arteriovenous communications.[4] A double lumen intra-aortic balloon was used to close the intimal entry tear in Shumway type B dissections.[5]

In the present case, the risk of the balloon causing an embolism into the aorta was accepted because of the deleterious effects of the persisting fistula. The surgical mortality for repair of a type A aortic dissection is 15–20%[1]; haemorrhage from suture lines in friable aortic tissues contributes significantly.[2] Decompression of the para-aortic lumen into the right atrium can be a lifesaving procedure; a method by which the resulting fistula can be closed later without surgery will be valuable.

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Br Heart J 1988;**60**:361

Correspondence

Vasculitis complicating treatment with intravenous anisoylated plasminogen streptokinase activator complex in acute myocardial infarction

Sir,

We were interested to read the report by Bucknall *et al* (1988;**59**:9–11) on vasculitic reactions after intravenous anisoylated plasminogen streptokinase activator complex (APSAC) in acute myocardial infarction. We report a similar reaction in patients treated with intravenous conventional streptokinase, which is a large component of the APSAC molecule.

Eight to ten days after intravenous streptokinase ($1{\cdot}5 \times 10^6$ units infused in one hour) four of 120 patients with myocardial infarction developed purpuric, vasculitic eruptions affecting the extensor surfaces of the legs. These resolved in 48 hours to two weeks. None had evidence of systemic effects. Skin biopsy specimens from the two most severely affected individuals were consistent with focal vasculitis, and direct immunofluorescent studies showed perivascular deposition of C3 and IgA. Urinalysis, autoantibody, and complement studies and indices of renal function were normal in all patients, but two patients had raised concentrations of serum immunoglobulins (one IgA and one IgG). Both these patients developed gammaglobulin paraprotein bands, which on isoelectric focusing were shown to be oligoclonal IgG bands. These abnormalities were not present six weeks later. All our patients had raised erythrocyte sedimentation rates (60 to 102 mm in the first hour) and a rise in antistreptolysin O titre after administration of streptokinase (from a mean of 80 to 175 U/l).

We have evidence that an immune reaction was the basis of this complication, namely an increase in antistreptolysin O titres from a baseline titre consistent with previous exposure to streptococcal protein; the deposition of IgA and C3 in the skin; and oligoclonal IgG bands on isoelectric focusing, which are all features of an immune response to antigenic challenge.[1] The delayed onset of these features is consistent with an immune complex mediated hypersensitivity reaction, and, although we did not detect circulating immune complexes, they were found in another study.[2]

These reactions occurred despite routine prophylaxis with 100 mg hydrocortisone and a single intravenous dose of chlorpheniramine (10 mg). This dose of hydrocortisone does not prevent immediate type hypersensitivity reactions,[3] and in our patients and others[4] it did not prevent delayed reactions.

In our experience, such complications are rare and without sequelae. Nevertheless, Bucknall's patients, unlike ours, showed multisystem effects, and crescentic glomerulonephritis has been reported after treatment with streptokinase and subsequent streptococcal infection.[4] Patients treated with streptokinase and APSAC should be monitored closely. As the use of these agents increases in acute myocardial infarction we expect that the numbers of such reactions will increase.

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Notices

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 22 to 24 November 1988. The closing date for receipt of abstracts was 24 June 1988.

The Annual General Meeting for 1989 will take place in Oxford on 6 and 7 April 1989, and the closing date for receipt of abstracts will be 6 January 1989.

Coronary arteriography

The 3rd International Symposium on Coronary Arteriography will take place in Rotterdam on 18 to 20 June 1989. Inquiries to Office for Post Graduate Medical Education, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands.

Echocardiology

The 8th Symposium on Echocardiography will take place in Rotterdam on 21 to 23 June 1989. Inquiries to Office for Post Graduate Medical Education, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands.

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British Heart Journal

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Editorial

Silent ischaemia: clinical implications in 1988

K M FOX

From the National Heart Hospital, London

Within the past few years the concept of silent ischaemia has become widely known. But silent ischaemia is not a new finding. Paul Wood and his colleagues described the development of electrocardiographic changes during exercise testing in the absence of chest pain and suggested that this could represent latent angina.[1] In 1974 Stern and Tzivoni described asymptomatic alteration in the ST segment recorded during ambulatory monitoring in patients with coronary artery disease.[2] Subsequent studies showed that such ST segment changes were common.[3 4] Initially, concern that these ST segment changes represented a "false positive" response was fuelled by the debate over the use and value of exercise testing as a diagnostic tool.[5 6]

Later, invasive monitoring in the catheter laboratory, positron tomography, and ambulatory pulmonary artery monitoring showed that most of these episodes of ST segment depression reflect myocardial ischaemia,[7–9] and it has been proposed that routine clinical management of patients with angina pectoris should include the identification and treatment of silent ischaemia. In the United Kingdom, however, routine ambulatory monitoring to detect and treat silent ischaemia is seldom performed.

It has been suggested that about 60–80% of patients with chronic stable angina have silent ischaemia.[3 10] Unfortunately, most of these data were obtained from highly selected patient populations. Recently we studied 150 unselected patients with angina pectoris on no medical treatment.[11] Silent episodes of ST segment depression were about three times as frequent as angina pectoris: one third of the patients had both silent episodes and painful episodes of ST segment depression and 20% had silent episodes without angina pectoris. Also, about a third of the patients had 90% of the silent episodes of ST segment depression. So silent ischaemia is most likely to be important in about one third of patients with chronic stable angina; other workers also have come to similar conclusions.[12]

This does not imply that silent ischaemia is unimportant. In the United Kingdom about a million patients have chronic stable angina and so about 300 000 would have frequent episodes of silent ischaemia. But these data came from patients with chronic stable angina who were not on medical treatment and who had cardiac catheterisation. Similar studies have not been performed in medically treated patients with stable angina; such patients are likely to have fewer episodes of silent ischaemia.

Workers who compared changes in heart rate with changes in the ST segment during ambulatory monitoring and exercise testing concluded that silent ischaemia is predominantly related to an alteration in coronary blood flow.[3 7 13] But analysis of the heart rate during silent episodes and painful episodes of ST segment depression during ambulatory monitoring does not support this conclusion.[14] The 24 hour diurnal distribution of silent and painful ischaemia is similar; in patients with chronic stable angina there are more episodes between 9 am and 10 pm than during the rest of the day and night,[3 15] while in patients with variant angina, silent episodes and painful episodes are most common at night.[16] Analysis of heart rate changes has shown that both silent episodes and painful episodes of ST segment depression can on occasion be preceded by increase in the heart rate while other episodes within the same patient are not. Mental stress can provoke myocardial ischaemia; often this is silent.[17] The pathophysiological mechanisms for this picture are unclear but an increase in myocardial oxygen demand and coronary vasoconstricion are likely to be important. Thus in chronic stable angina, silent ischaemia could be caused by various mechanisms as is angina pectoris. These mechanisms will vary from patient to

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patient and even from hour to hour within the same patient. The prediction that if the pathophysiological mechanisms of silent ischaemia and angina are similar both conditions will respond to the same treatment is borne out by reports that drugs that relieve angina can also suppress silent ischaemia.[18-20]

Although silent ischaemia can be treated with antianginal agents it is still far from certain that such treatment is necessary or justifies the extra cost and staff it would require. Silent ischaemia is best identified by 24 hour ambulatory monitoring of the electrocardiogram. Amplitude modulated systems give a more stable baseline and are more widely available but frequency modulated systems give a more appropriate frequency response.[21] The new generation of solid state systems that are now available gives computerised reports and these need little attention from a technician.[22] Although solid state systems are less labour intensive they require validation and they are expensive.

Must ambulatory monitoring be used to identify silent ischaemia? Perhaps the investigations could be targeted more appropriately? Selwyn and Ganz suggested that angina pectoris does not reflect the true severity of myocardial ischaemia and that ambulatory monitoring may be needed to identify those patients with the worst prognosis.[23] But in the same issue of the *New England Journal of Medicine*, Epstein *et al* claimed that electrocardiographic monitoring added little to the prognostic information provided by exercise testing.[24] Certainly, silent ischaemia is rare in those patients with a negative exercise test and in those whose exercise test is positive only at high workload.[11 25 26] Also there seems to be a close linear correlation between the time to 1 mm ST segment depression recorded during exercise testing and the frequency of silent ischaemia; perhaps therefore ambulatory monitoring could be restricted to those patients with ST segment depression at low workloads on the exercise test.

Although silent ischaemia can be treated and the use of exercise testing with ambulatory monitoring might not overstretch resources, we still do not know whether silent ischaemia in patients with chronic stable angina should be identified and treated. Prognostic data are woefully lacking. In the 1970s Erikssen *et al* investigated 2014 symptom free male factory workers by exercise testing and coronary angiography.[27] Fifty men had a positive exercise test and confirmed coronary artery disease without chest pain. In the next eight years 10 (20%) developed an acute myocardial infarction or died. But it is still not certain that these subsequent cardiovascular events had anything to do with silent ischaemia; they may have merely reflected the underlying coronary artery disease. More importantly, would treatment of silent ischaemia have prevented these events? Acute myocardial infarction is usually caused by rupture of an atherosclerotic plaque and the same mechanism almost certainly causes sudden death.[28] What effect will antianginal agents have? At the present time there is no evidence to suggest that preventing ischaemic episodes either by reduction of myocardial oxygen demand or by increasing coronary blood flow will have any effect on plaque rupture and thrombosis. Perhaps the frequency of silent ischaemia together with a diminution of exercise tolerance are markers that a stable plaque has become unstable; in such circumstances it might be better to stabilise the plaque and thrombotic process with drugs that prevent surges in blood pressure, smooth muscle relaxants, antithrombotic and anti-platelet agents, or to operate or perform angioplasty.

Another suggestion is that repeated episodes of myocardial ischaemia lead to small areas of myocardial cell death and subsequent reduction of left ventricular function.[29] If this is true, drugs that reduce the frequency and duration of silent ischaemic insults may be beneficial. Preliminary data support this theory,[30] but further studies are needed to resolve the question.

In contrast, in unstable angina evidence suggests that episodes of painful and silent ischaemia do have important prognostic implications. Gottlieb and his co-workers showed that silent ischaemia in patients with unstable angina was associated with an increased number of cardiovascullar events, particularly myocardial infarction and death.[31] The most likely mechanism for the angina that precedes infarction is an unstable plaque with superadded platelet aggregation and possibly thrombosis.[28] Appropriate treatment of such ischaemia may prove rewarding. Again, however, although drugs that reduce myocardial oxygen demand and smooth muscle relaxants permit the myocardium to withstand greater ischaemic insults, they are unlikely to prevent myocardial infarction. In the recent Holland Interuniversity Nifedipine/Metoprolol trial the risk ratio of preventing acute myocardial infarction with β blocker alone was 1·07 and that for calcium antagonist was 1·51.[32] The use of drugs or interventions that directly influence the pathogenesis may, therefore, have to be considered—such as antiplatelet agents, coronary angioplasty, and bypass surgery.[33] Most clinicians would probably consider exercise testing unwise in patients with unstable angina, and repeated ambulatory monitoring to assess the frequency, duration. and severity of silent and painful ischaemia may well prove to be the most suitable investigation.

Silent ischaemia may be an important feature for identifying patients who will require further investigation and careful consideration of treatment. But much of this is speculation and until firm data have been collected routine ambulatory monitoring of the ST segment cannot be advised. In the United States there are devices (Q Med) to monitor the ST segment; ST segment depression sets off an alarm that prompts the patient to take a tablet of glyceryl trinitrate.[22] The barometer of silent ischaemia has yet to settle; I hope that it will not be at this extreme.

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Coronary angioplasty in unstable angina and stable angina: a comparison of success and complications

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SUMMARY One hundred and five patients with unstable angina and 175 with chronic stable angina were treated by primary percutaneous transluminal coronary angioplasty. Patients with unstable angina had had symptoms for a shorter time and were more likely to have angiographically complex lesions and lesions < 10 mm in length than patients with chronic stable angina. Other baseline variables were not significantly different in the two groups. The overall primary success rate was similar in both groups (87% *v* 86%). Nine of the 14 unsuccessful procedures in those with unstable angina and nine of the 24 unsuccessful procedures in those with stable angina were the result of acute occlusion. These results led to a 9% frequency of procedure related myocardial infarction in patients with unstable angina and a 5% rate in those with stable angina (NS). The procedure related infarct rate tended to be higher in patients with unstable angina who had coronary angioplasty soon after an episode of unstable angina (mean 10 days) than in those in whom it was delayed (mean 35 days) (12% *v* 3%) (NS). In patients with unstable angina who had had a previous myocardial infarction procedure related infarction was significantly more common (18%) than in patients with no previous myocardial infarction (3%). The difference between those with and without previous infarction was also significant in patients with stable angina (10% *v* 3%).

The term unstable angina has been used to describe a wide range of chest pain syndromes in differing clinical contexts. Other terms that have been used include acute coronary insufficiency, pre-infarction syndrome, crescendo angina, and post-infarction unstable angina. Unstable angina is defined as ischaemic chest pain, either at rest or on minimal exertion, lasting longer than 15 minutes with no evidence of infarction. The condition was associated with a high mortality in the first year after the unstable event—ranging from 10% to 40% depending on the particular subgroup studied.[1-4] In most of these studies patients were on vigorous medical treatment. Only aspirin has been shown conclusively to be effective; it reduced the rate of myocardial infarction and the mortality by about half.[5] While coronary artery bypass grafting has been shown to improve functional class and symptoms in patients with unstable angina, randomised studies have shown no overall improvement in mortality or myocardial infarction in surgically treated patients compared with medically treated patients,[6 7] and the surgical mortality in these patients is high.

Since the advent of coronary angioplasty ten years ago, the scope of the technique has been broadened to include various subgroups of patients with unstable angina of varying severity.[8-11] The primary success rate is high, but acute major complications seem to be more common in patients with unstable symptoms than in those without.

We have examined the reasons for failure in our series of patients undergoing primary percutaneous transluminal angioplasty for clinically severe unstable angina and we compared the results with those in patients having the procedure for chronic stable symptoms. The procedure may fail because the target lesion cannot be crossed or because of vessel occlusion despite an initial uneventful dilatation. We also discuss the frequency and sequelae of acute occlusion in the two groups of patients in the light of our current understanding of unstable and stable angina.

Patients and methods

PATIENTS

There were 300 coronary angioplasty procedures at

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Table 1 *Baseline characteristics and angiographic details in patients with unstable angina and stable angina*

	Unstable	*Stable*	*Total*
No (%)	105 (35)	175 (65)	280 (100)
M:F	3:1	4:1	3 7·1
Mean age (yr)	47	52	50
Mean duration	8*	27*	19
Target vessel:			
LAD (n (%))	62 (59)	98 (56)	160 (57)
RCA (n (%))	29 (28)	55 (31)	84 (30)
Cx (n (%))	11 (10)	19 (12)	30 (11)
Graft (n (%))	3 (3)	3 (1)	6 (2)
Multivessel (n (%)	13 (12)	13 (7)	26 (9)
Unattempted occlusion	4 (4)	15 (9)	19 (7)
Characteristics of stenosis:			
Percentage narrowing (mean (SD))	70 (10)	76 (8)	74 (9)
Concentric (n (%))	85 (72)	124 (66)	209 (68)
Eccentric (n (%))	33 (28)	64 (34)	97 (32)
< 10 mm long	85 (72)	86 (46)	171 (56)
> 10 mm long	33 (28)*	102 (54)*	135 (44)
Complex (n (%))	39 (33)*	30 (16)*	69 (23)
Occluded (n (%))	4 (4)	10 (6)	14 (5)

*p < 0 001.
LAD, left anterior descending; RCA, right coronary artery; Cx, circumflex.

the Queen Elizabeth centre between May 1983 and May 1987. Two hundred and eighty were primary procedures and all of them were performed by one of two principal operators. In 105 of the primary procedures the patients were classed as having unstable angina. All 105 had ischaemic chest pain at rest that lasted for > 15 minutes and led to their admission to hospital, with or without ST/T wave changes on the electrocardiogram but with no new Q wave formation, and without a diagnostic rise in cardiac enzymes. All the patients were admitted first to a coronary care unit with a suspected diagnosis of acute myocardial infarction. All received multiple antianginal medications because they continued to have chest pain at rest or on minimal exertion. Most (69) had recurrent chest pain requiring intravenous nitrates, and they could not be mobilised or discharged home before investigation and further intervention. The remainder (36) improved initially on medical treatment and they had coronary angiography and subsequently coronary angioplasty if they continued to have symptoms after they were mobilised.

Of those with unstable angina, 46 had a history of angina of less than one month or the episode of unstable pain was the first manifestation of ischaemic heart disease. Thirty eight (36%) of those with unstable angina had already had a myocardial infarction. Most of these (30) had sustained their infarct at least three months before the episode of unstable angina. In six patients the myocardial infarct occurred within one month but not less than one week before their angioplasty. Twenty two (21%) had had a Q wave infarction and 16 (15%) a non-Q wave infarction.

The remaining 175 patients had chronic stable angina. Of these, 63 (36%) had had a previous myocardial infarction at least three months before the procedure—45 (26%) with Q wave infarct and 18 (10%) non-Q wave. All these patients had severe chronic stable angina on effort despite antianginal medications. Most 82 (81%) of the total of 101 patients with previous infarction had angioplasty to the infarct related vessel—34 (90%) of the 38 with unstable angina and 48 (76%) of the 63 with stable angina. The remainder had angioplasty to a non-infarct related vessel.

Table 1 shows the baseline patient characteristics in the two groups. There were no significant differences in mean age, ratio of men to women, or target vessel between the two groups, although the proportion of diseased left anterior descending arteries was higher in patients with unstable angina. The duration of anginal symptoms was significantly shorter in those with unstable angina (8 *v* 27 months; χ^2 = 11·15, p < 0·001). Four patients with unstable angina and 15 with stable angina had occluded arteries that were not the primary target vessel and were not attempted. These were patients with previous infarction who had angioplasty of a non-infarct related vessel as discussed above. Fourteen patients had occluded target vessels: four with unstable angina and 10 with stable angina. Eleven of these 14, two with unstable angina and nine with stable angina, had had a previous infarct.

The stenosis of the target vessel was assessed in two orthogonal planes and characterised according to its length (< or ⩾10 mm) and shape—concentric, eccentric, complex, or occluded. Length was assessed in the projection showing the longest aspect of the lesion. An eccentric stenosis was defined as one in which the lumen lay within one half of the putative normal lumen in at least one projection. A lesion was called complex if there was evidence of intraluminal clot, irregularity of the borders, or if it occurred on a bend of > 45°. The severity of stenoses and the ratio of concentric to eccentric lesions were similar in both groups. In patients with unstable angina there were significantly more complex lesions (33 *v* 16%; χ^2 = 12·95, p < 0·001). There were significantly more lesions > 10 mm in length in those with stable angina (54 *v* 28%; χ^2 = 11·15, p < 0·001). Twenty six patients (13 in each group) had a second vessel dilated as well as the primary target vessel and the characteristics of stenosis apply to all attempted vessels.

CORONARY ANGIOPLASTY

Angioplasty was performed via the transfemoral route in all but two patients and a steerable balloon catheter system was used in all except the first 20 patients. All patients were treated with nifedipine (10 mg three times a day), isosorbide dinitrate (10 mg three times a day), and aspirin (300 mg daily) for at least 48 hours before the procedure if they were not already established on such treatment. During the procedure patients were heparinised and maintained on an infusion of isosorbide dinitrate. In patients with stable angina heparin was stopped after angioplasty, but in those with unstable angina it was continued as an infusion for 24 hours. Balloon inflation times and pressures varied with clinical circumstances, the angiographic result, and the improvement in transstenotic pressure gradient. In all patients in whom acute coronary occlusion occurred repeat angioplasty was immediately attempted. If this was unsuccessful patients were considered for emergency coronary artery bypass grafting.

A successful procedure was defined as a reduction in stenosis to $<50\%$ of the diameter of the nearest normal vessel segment in the absence of a major complication—that is, procedure related myocardial infarction, coronary artery bypass grafting, or death.

We used the Minitab statistics package (Minitab Inc, State College, PA 16801, USA) for statistical analysis. Differences between the groups and in baseline data were compared by χ^2 testing and unpaired Student's t testing as appropriate.

Results

SUCCESS RATE

The overall primary success rate was similar in both groups (unstable angina 87%; stable angina 86%). Over the four year period of the study the success rate of the entire series improved from 80% to 92% (table 2) but there was no significant difference in success rate between patients with unstable angina and those with stable angina in any year. The proportion of patients with unstable angina increased significantly from 20% in 1983/84 to 43% in 1986/87 ($\chi^2 = 8{\cdot}36$, $p < 0{\cdot}01$).

Table 3 *Success rates, reasons for failure, and final outcome in the two groups*

	Unstable	*Stable*
No (%)	105 (35)	175 (65)
Success (n (%))	91 (87)	151 (86)
Failure (n (%))	14 (13)	24 (14)
Reason for failure:		
Occlusion (n (%))	9 (9)	12 (7)
Failure to cross (n (%))	5 (4)	12 (7)
Final outcome		
MI (n (%))	9 (9)	9 (5)
Death	2	1
CABG	4	4

MI, myocardial infarction; CABG, coronary artery bypass grafting.

REASONS FOR FAILURE

Table 3 shows the overall success rate and reasons for failure. A greater proportion of failures in those with unstable angina were caused by acute occlusion rather than failure to cross the stenosis (9% *v* 4%) whereas the same proportion of failures were caused by these two factors (7% *v* 7%). In all patients with unstable angina the outcome of acute occlusion was an acute procedure related myocardial infarction, despite attempts at immediate re-angioplasty or referral for emergency operation. These results led to a 9% frequency of acute infarction in patients with unstable angina compared with 5% in those with stable angina. Two of the three deaths in the series were in patients with unstable angina. Four patients in each group had emergency coronary artery bypass grafting.

TIMING OF INTERVENTION

Sixty nine (68%) of the patients with unstable angina had early coronary angioplasty at a mean interval of 10 days after the episode of unstable angina because despite intensive medical treatment they had continuing rest pain or severe angina limiting mobilisation. The remaining 36 (32%) were mobilised on medical treatment and had coronary angioplasty at a mean interval of 35 days after the episode (table 4). The success rates in these two subgroups of patients with unstable angina were similar (87% *v* 84%). Nearly all the failures in those who had early treatment were caused by acute occlusion. Only one patient who was

Table 2 *Increase in proportion of patients with unstable angina and annual success rate in both groups throughout the series*

	1983/84		*1984/85*		*1985/86*		*1986/87*	
	Unstable	*Stable*	*Unstable*	*Stable*	*Unstable*	*Stable*	*Unstable*	*Stable*
Success (n (%))	9 (82)	36 (80)	12 (80)	30 (79)	33 (87)	34 (92)	37 (90)	51 (93)
Failure (n (%))	2 (18)	9 (20)	3 (20)	8 (21)	5 (13)	3 (8)	4 (10)	4 (7)
Total (n (%))	11 (20)	45 (80)	15 (28)	38 (72)	38 (51)	37 (49)	41 (43)*	55 (57)*
Success rate (%)	82	80	80	79	87	92	90	93
Overall success (%)	80		79		89		92	

*p < 0·01.

Table 4 *Success and reasons for failure in patients with unstable angina that was treated early and late after the unstable event*

	Early (10 days)	*Late (35 days)*
No (%)	69 (66)	36 (34)
Success (n (%))	60 (87)	31 (86)
Failure (n (%))	9 (13)	5 (14)
Reason for failure		
Occlusion (MI) (n (%))	8 (12)	1 (3)
Failure to cross (n (%))	1 (1)	4 (11)

MI, myocardial infarction.

treated later had acute occlusion; the predominant cause of failure in this group was difficulty in crossing the lesion. The numbers are small and the differences are not statistically significant.

PREVIOUS MYOCARDIAL INFARCTION

Table 5 shows the relation of previous myocardial infarction to success in the groups with unstable or stable angina. The proportions of patients with unstable angina and with stable angina who had had a previous myocardial infarction were the same (36%). In both groups the rate of procedure related myocardial infarction was significantly higher in patients with previous myocardial infarction: 18 *v* 3% (χ^2 = 7·49; $p < 0{\cdot}01$) in unstable angina and 10 *v* 3% (χ^2 = 3·91; $p < 0{\cdot}05$) in chronic stable angina. There was no significant difference between the groups with unstable and stable angina with previous myocardial infarction.

Discussion

We retrospectively reviewed our series of patients who had coronary angioplasty and we specifically examined the success rate and reasons for failure in patients with unstable angina and compared them with those in patients with chronic stable angina. The overall success rate was similar in both groups of patients, but in patients with unstable angina failure was more likely to be caused by acute occlusion and consequent procedure related myocardial infarction rather than failure to cross the lesion. Patients with unstable angina who needed urgent treatment for continuing symptoms seemed to have a higher rate of acute occlusion than patients whose symptoms were controlled by medical treatment. Patients in both angina groups who had sustained a previous myocardial infarction had a significantly lower success rate and a higher frequency of acute occlusion; the resulting rates of procedure related infarction were 18% in patients with unstable angina and 10% in those with stable angina.

Table 5 *The influence of previous myocardial infarction on success and failure of angioplasty in both groups*

	Unstable (105)		*Stable (175)*	
	Previous MI	*No previous MI*	*Previous MI*	*No previous MI*
No (%)	38 (36)	67 (64)	63 (36)	112 (64)
Success (n (%))	29 (76)	62 (92)	49 (78)	102 (91)
Failure (n (%))	9 (24)*	5 (8)*	14 (22)†	10 (9)†
Reason for failure.				
Acute occlusion (MI) (n (%))	7 (18)	2 (3)	6 (10)	3 (3)
Failure to cross	2 (6)	3 (5)	8 (12)	7 (6)

*p < 0 01; †p < 0·05.
MI, myocardial infarction.

Patients with unstable angina form a heterogeneous group containing those with recent onset angina (presenting as a first ischaemic event), patients with pre-existing exertional angina that has become unstable, and patients who have sustained a previous myocardial infarction. None the less, we believe that our patients presented with a relatively uniform clinical problem. Whatever the preceding history, whether it was recent onset angina, previously chronic stable angina, or previous myocardial infarction, all these patients presented with an episode of rest pain thought initially to be caused by myocardial infarction; hence their admission to a coronary care unit. Because patients in these different subgroups may have a different prognosis if they remain untreated we have examined the results of angioplasty according to subgroup. Most patients required early intervention because intensive medical treatment failed to control their symptoms. Even patients in whom medical treatment, including aspirin, controls their symptoms have an event rate of up to 12%[12] if they remain on medical treatment.

The patients discussed here are pre-selected groups in that their coronary artery structure was regarded as being suitable for angioplasty. This explains the low rate of occlusion in target vessels in 101 patients who had already had an infarction. We did not attempt 19 occlusions and some of these patients had had non-Q wave infarcts. Their subsequent clinical course indicates that most of the patients with unstable angina were at increased risk; the event rate in the subsequent year was 40%.

Any analysis of a series of patients treated by coronary angioplasty must take into account the influence of improving operator experience and any changes in practice during the study period. Table 2 shows that the overall success rate improved over the four year period as the experience of the operators increased and equipment improved. The success rates in the two subgroups with unstable and stable angina remained similar throughout the period, even though the proportion of patients with unstable angina increased (20% in 1983/84 and 43% in 1986/87) after it was recognised that coronary angioplasty is successful in many patients with unstable angina.

Although the overall success rate was high in patients with unstable angina, procedure related myocardial infarction was more common than in patients with chronic stable angina, especially in patients with severe disease—that is, those who were treated early. The suggested mechanism for the development of unstable angina is rupture of an atheromatous plaque with subsequent platelet aggregation and thrombosis, and possibly superimposed coronary spasm.[13 14] Analysis of the coronary arteriograms of our patients showed that patients with unstable angina had a significantly higher proportion of complex lesions (33 *v* 16%; $\chi^2 = 10{\cdot}72$, $p < 0{\cdot}001$). We believe this is likely to have contributed to the higher rate of acute occlusion within the group with unstable angina. There was no direct correlation between patients with abnormal arteriograms and failed procedures, but these numbers are small. We assessed the complexity of lesions by the method used by Ischinger *et al*, who suggested that a complex angiographic lesion may be a risk factor for dissection or acute occlusion, though the predictive value of this index was low.[15] The presence of intraluminal thrombus on angiography may depend on the timing of the angiogram in relation to an episode of unstable angina because a longer interval will give more opportunity for resolution of the thrombus. There is no satisfactory explanation for the higher rate of acute occlusion when there is angiographic evidence of intraluminal thrombus. The thrombus itself is rarely evident after angioplasty either in the lesion itself or in the vessel beyond. It could be that the recently ruptured plaque predisposes the vessel to extensive dissection with the associated risk of vessel occlusion. The only other significant difference in coronary artery structure is that patients with stable angina had longer stenoses (54 *v* 28% > 10 mm). This may explain why failure was the result of difficulty crossing the lesions in a higher proportion of patients with stable angina.[16]

The failure rate owing to acute occlusion was significantly higher in all patients (both groups) who had had a previous myocardial infarction, as we have reported before.[17] It is possible that as well as an underlying susceptibility to plaque rupture these patients also have a poorly developed collateral circulation in the areas surrounding the infarcted zone.

The overall frequency of acute occlusion and consequent procedure related myocardial infarction in our study seems to be slightly higher than in other series of percutaneous transluminal coronary angioplasty in unstable angina,[9 10 18] though it resembles that reported by the National Heart, Lung and Blood Institute registry.[19] In the absence of previous infarction or in patients treated later after their episode of unstable angina the procedure related infarction rate is low and similar to that in patients undergoing angioplasty for chronic stable symptoms. As discussed above, we believe many of our patients were at high risk and that early intervention was unavoidable in most.

The overall 9% procedure related myocardial infarction rate for angioplasty in patients with unstable angina should be viewed in the light of the known high subsequent infarction rate on medical treatment. It is clear that some subgroups have a higher risk of infarction at angioplasty than others and it is one of the aims of this paper to try to identify some of the relevant risk factors. It may be that the group with the highest complication rate (18%) should have been treated by coronary artery bypass grafting, but published data show that mortality at operation is 5% compared with 2% at angioplasty, and there are few data on the frequency of perioperative infarction. Ideally, a randomised study based on intention to treat should be carried out to compare percutaneous transluminal coronary angioplasty with medical and surgical treatment and to explore both the short and long term benefits of the procedure. In our study clinical follow up of patients with unstable angina (1–3 years, mean 16 months) shows that only one of the patients in whom angioplasty was successful has had a myocardial infarction and there have been no late deaths. Our results support reports from other centres that coronary angioplasty is an appropriate treatment in selected patients with unstable angina.

In conclusion, it seems that various subgroups of patients with unstable angina can be successfully treated by coronary angioplasty. In this series acute procedure related myocardial infarction was more common in patients with unstable angina than in patients with stable angina. This was because patients with unstable angina had more severe symptoms that required early intervention. We believe that this reflects the unstable nature of a recently ruptured plaque with a raw thrombogenic surface. While coronary angioplasty is a useful option and has a high overall success rate in patients with unstable angina, careful risk analysis should be undertaken for all patients.

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Coronary artery calibre after direct intra-arterial infusion of epoprostenol (prostacyclin)

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SUMMARY Because epoprostenol (prostacyclin) is a prostaglandin that causes vasodilatation and inhibits platelet function it may be of benefit during coronary artery angioplasty. The safety and capacity of intracoronary epoprostenol to dilate coronary arteries were assessed in 16 patients undergoing routine coronary angiography. The view that best displayed the left epicardial coronary arteries was selected as a control for each patient. Intracoronary epoprostenol was then given and the angiogram was repeated in the chosen view. The procedure was repeated twice: once with a higher dose of epoprostenol and once after intracoronary isosorbide dinitrate. Angiograms were coded and analysed by an observer who was unaware of the treatment. The calibre of the arteries was measured from traced projections of the angiograms. The blood pressure, heart rate, and electrocardiogram were recorded throughout. The first two patients were given epoprostenol infusions of 2·5 and 5·0 ng/kg per minute to assess safety, and there were no untoward reactions. The next ten patients had epoprostenol infusions of 5·0 and 7·5 ng/kg per minute followed by intracoronary isosorbide dinitrate. No haemodynamic disturbances occurred and coronary luminal calibre did not change with epoprostenol (mean (SD) luminal diameter: 2·85 (0·62) mm control, 2·80 (0·61) mm at 5·0 ng/kg, and 2·80 (0·54) mm at 7·5 ng/kg), but it did increase significantly with isosorbide dinitrate (to 3·17 (0·36) mm). The last four patients had epoprostenol infusions of 7·5 and 10 ng/kg followed by intracoronary isosorbide dinitrate and two of them became hypotensive (one after epoprostenol and one after isosorbide dinitrate). Coronary luminal calibre did not change significantly (3·5 (0·45) mm control, 2·96 (0·81) mm at 7·5 ng/kg, 3·45 (0·96) mm at 10 ng/kg, and 3·20 (0·61) mm with isosorbide dinitrate). Eight patients developed tall T waves on the electrocardiogram during epoprostenol infusion but none had arrhythmias.

The results indicate that clinically tolerable doses of intracoronary epoprostenol do not significantly dilate the epicardial coronary arteries. This route of administration is therefore unlikely to be of use during coronary angioplasty, although the antiplatelet action of intravenous epoprostenol might help to prevent restenosis.

Prostacyclin is a naturally occurring prostaglandin (PGI_2) synthesised by endothelial cells that has profound inhibitory effects on platelet aggregation.[1] It is also a potent vasodilator and it has been used as a therapeutic agent (epoprostenol) to treat atherosclerotic peripheral vascular disease[2] and pulmonary hypertension.[3] Epoprostenol may be useful during and after transluminal coronary angioplasty because both coronary artery dilatation and inhibition of platelet aggregation may be of benefit during this procedure. Epoprostenol dilated canine coronary arteries,[4] and intracoronary infusions in man seem to be safe,[5] but the effects on the diameter of human coronary arteries are not known. We have studied the effect of intracoronary epoprostenol on human coronary arteries.

Patients and methods

PATIENTS

We studied 16 patients (13 men and three women; mean age 52·7) undergoing routine coronary angiography. Patients were admitted 48 hours before

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the study so that all medication could be stopped. Patients who had attacks of angina were treated with sublingual glyceryl trinitrate. Patients gave their informed consent and the study was approved by the Leeds Western District Research Ethics Committee.

CORONARY ANGIOGRAPHY

Angiography of the left ventricle and coronary arteries was performed from the femoral approach. The images were obtained with a dedicated Phillips angiographic system (9 inch by 5 inch) and they were recorded on Kodak CFE or RAR film at 30 frames per second with an Arritechno camera. All patients were given sodium heparin (1500 IU) via the catheter before angiography. Non-ionic contrast medium (iopamidol 370) was used in each case. Video recordings of the standard *x* ray projections were reviewed and the projection most clearly displaying the proximal parts of the left coronary artery was selected. Heart rate and systemic arterial blood pressure were recorded continuously throughout the procedure, and after a minimum of five minutes' equilibrium the left coronary angiogram was recorded in the chosen projection. The film was marked with a two letter code chosen by the radiographer. After the return of heart rate and blood pressure to control values, the first infusion of epoprostenol (50 ml) was delivered via the left coronary angiographic catheter at 50 ml/min. One minute after the infusion, the coronary angiogram was repeated under identical conditions to the control injection. The film was again marked with a double letter code. After a further five minutes, the second infusion of epoprostenol (50 ml) was administered and the coronary angiogram was repeated one minute later. The film recording the cumulative effect of both doses was marked with a third code. The final infusion consisted of 100 μg of isosorbide dinitrate in 20 ml of 0·154 mol/l sodium chloride administered two minutes after the last epoprostenol infusion, and the coronary angiogram was repeated to give a fourth coded film.

DRUG INFUSIONS

The sodium salt of prostaglandin (epoprostenol, Wellcome Foundation) stored as a freeze dried powder was dissolved in glycine buffer (pH 10·5) to make a concentrated solution of 10 000 ng/ml. Immediately before infusion this was further diluted with glycine buffer to a concentration of 20 ng/ml. The final dilutions were made with 0·154 mol/l sodium chloride to a maximum ratio of six volumes of saline to one volume of epoprostenol to maintain an alkaline pH.

The first two patients in the study were given low dose intracoronary infusions of epoprostenol (2·5 and 5·0 ng/kg per minute) to check safety. The next ten patients had infusions of 5·0 and 7·5 ng/kg per minute (group 1) and the final four patients had infusions of 7·5 and 10·0 ng/kg per minute (group 2). All patients, except the first two, had additional infusions of isosorbide dinitrate (100 μg in 20 ml 0·154 mol/l sodium chloride). One patient was also given an infusion of the buffer alone.

MEASUREMENT OF THE DIAMETER OF THE LUMEN OF THE EPICARDIAL CORONARY ARTERIES

Of the 16 patients studied, all but one had coronary artery disease. Seven patients had two vessel disease, six patients had three vessel disease, and two patients had single vessel disease. Only normal segments of coronary artery were chosen for measurement.

The angiographic recordings were coded and the code was not broken until all the film measurements had been made consecutively at the end of the study. The 35 mm cine films were viewed on a Tagarno projector, and the luminal diameter of the coronary artery was determined by tracing on to paper a chosen part of the vessel from end diastolic frames and measuring this directly with a calibrated eye glass (Flubacher, Switzerland). The catheter (of known diameter) was also traced from the same angiographic frame to provide a measure of magnification. All measurements were made by the same observer (JW). The method was similar to that used by Meier *et al.*[6] We compared the coronary artery luminal diameters by Friedman's analysis of variance.

Results

LUMINAL DIAMETER OF THE CORONARY ARTERY

The ten patients in group 1 had intracoronary epoprostenol infusions of 5·0 and 7·5 ng/kg per minute and no significant changes were seen in the luminal calibre. After infusion of isosorbide dinitrate, however, the calibre of the lumen increased by 11% compared with the control values ($p < 0·02$) (table). One patient in this group had an additional infusion of buffer solution alone, which did not change the luminal calibre (control 2·39 mm,

Table *Intraluminal diameter of epicardial coronary arteries after intracoronary infusion of epoprostenol (PGI_2)*

	Mean (SD) coronary artery diameter (mm)			
	Control	*1st infusion*	*2nd infusion*	*Isosorbide dinitrate*
Group 1 (10 patients)	2·85 (0·62)	2·80 (0·61)	2·80 (0·54)	3·17 (0 36)*
Group 2 (4 patients)	3 50 (0 45)	2 96 (0·81)	3 45 (0·96)	3·20 (0·61)†

*p < 0 02; †three patients.

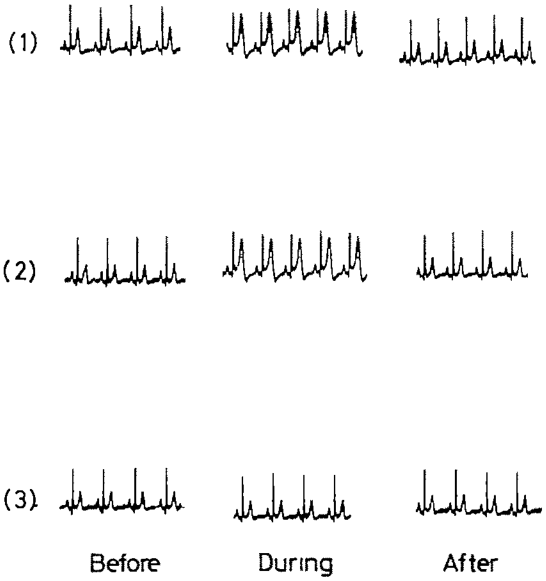

Figure *Electrocardiograms before, during, and after intracoronary infusion of epoprostenol in buffer solution (1), of buffer solution alone (2), and of contrast medium (3).*

epoprostenol 2·46, isosorbide dinitrate 2·60, buffer 2·51 mm).

Patients 1 and 2 from group 2 showed the same response as the patients in group 1. Patient 3 was the only patient to show an increase in coronary artery calibre after epoprostenol infusion, but soon after the infusion he became hypotensive and nitrate was not given. Patient 4 showed no response to epoprostenol and became hypotensive soon after the nitrate infusion.

HAEMODYNAMIC FUNCTION AND ADVERSE EFFECTS

In the first two patients studied low dose intracoronary infusions of epoprostenol had no untoward side effects.

The drug was generally well tolerated but had side effects at doses > 7·5 ng/kg per minute. Of the two patients in group 2 who became hypotensive, only one had symptoms, which responded to simple leg raising. No patients in group 1 experienced hypotension. Three of the patients experienced facial flushing, unrelated to the dose. Eight patients developed pronounced T wave peaking on the electrocardiogram during infusion of epoprostenol, which was not seen during infusion of either contrast or isosorbide, but it was seen after infusion of the buffer (figure). In two further patients T wave inversion developed during epoprostenol infusion, which also occurred with contrast and isosorbide infusion. Both of these patients had severe coronary artery disease.

Discussion

The results indicate that intracoronary epoprostenol does not dilate the epicardial coronary arteries. The lack of response to epoprostenol was not caused by the inability of the diseased vessels to respond, because subsequent infusion of isosorbide dinitrate significantly increased the luminal diameter. The apparent failure to respond to isosorbide among patients in group 2 was misleading; it was the result of small numbers and the failure of one patient to respond, probably because of compensatory vasoconstriction after hypotension. The doses tolerated in this study were slightly higher than those routinely given in peripheral intravenous infusions[7–9] but increasing the dose to 10 ng/kg per minute produced hypotension.

The study was carried out as a preliminary to investigating the use of epoprostenol given by intracoronary infusion during coronary artery angioplasty with the aim of promoting vasodilatation and inhibiting platelet function. Our results have shown that intracoronary epoprostenol does not increase the diameter of the epicardial coronary artery. Other investigators have shown an increase in coronary blood flow with intravenous epoprostenol[8] and intracoronary prostaglandin E_1,[10] probably caused by dilatation of the resistance vessels. Nitrates are customarily used during angioplasty to achieve maximal dilatation of the epicardial coronary artery, and it is unlikely that epoprostenol alone would achieve such an objective. Coronary artery dilatation might occur with higher doses of epoprostenol but the risk of inducing hypotension would be unacceptable (patient 3, group 2).

The inhibitory effect of epoprostenol on platelets has been seen with peripheral intravenous infusions,[11] and this combined with the antithrombotic effect of increased coronary flow[8] suggests that intracoronary administration is unlikely to have any added benefit.

Intracoronary infusions of epoprostenol were associated with T wave peaking and slight elevation of the ST segment. Although no arrhythmias were detected, these changes in the presence of "angioplasty induced ischaemia", are potentially hazardous. It seems that the electrocardiographic changes were directly related to the buffer, which is highly alkaline (pH ≃ 10·5) and which when infused on its own reproduced these changes. Eight of the patients who developed electrocardiographic changes had either two or three vessel coronary artery disease, and such ischaemic changes on the electrocardiogram might have been a consequence of a "steal" phenomenon,[8] although this seems unlikely because the buffer alone also produced a similar effect.

In conclusion, intracoronary infusion of epoprostenol is unlikely to confer any additional benefit over the effects of intravenous administration during angioplasty procedures. The data indicate that epoprostenol at tolerable doses cannot be used instead of nitrates for dilatation of the epicardial arteries. Any antithrombotic actions of the drug, which might help to reduce the incidence of restenosis associated with angioplasty, are just as likely to be achieved by peripheral intravenous infusion.

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Relative power of clinical, exercise test, and angiographic variables in predicting clinical outcome after myocardial infarction: the Newham and Tower Hamlets study

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SUMMARY The interrelations of clinical, exercise test, and angiographic variables and their relative values in predicting specific clinical outcomes after myocardial infarction have not been fully established. Of 302 consecutive stable survivors of infarction, 262 performed a predischarge submaximal exercise test. In the first year after infarction patients with a "positive" exercise test were 13 times more likely to die, 2·8 times more likely to have an ischaemic event, and 2·3 times more likely to develop left ventricular failure than patients with negative tests. Patients with positive exercise tests underwent cardiac catheterisation. Features of the history, 12 lead electrocardiogram, in-hospital clinical course, exercise test, and left ventricular and coronary angiograms that predicted these clinical end points were identified by univariate analysis. Then multivariable analysis was used to assess the relative powers of all variables in predicting end points. Certain features of the exercise test remained independent predictors of future ischaemic events and the development of overt left ventricular failure, but clinical and angiographic variables were more powerful predictors of mortality. Because the exercise test is also used to select patients for angiography, however, the results of this study strongly support the use of early submaximal exercise testing after infarction.

An early submaximal exercise test can detect high and low risk groups after acute myocardial infarction.[1-3] Although interactions between exercise and angiographic variables have been investigated in part,[4-6] the interactions between clinical and exercise variables are still unclear.[7] Prognosis is related to left ventricular dysfunction,[8 9] arrhythmias,[10 11] and the presence of certain patterns of coronary artery disease.[12 13] The relative powers of variables in predicting particular clinical outcomes must be assessed by multivariable (rather than univariate) analysis.

The results of any study of outcome of clinically stable survivors after myocardial infarction must take account of potential differences between the total population and the proportion that has been studied in depth; these differences are the most important factor in determining whether recommendations generated from the results of a study hold for all such survivors or whether they apply only to a small subset. We therefore designed this study to investigate the relative powers of clinical, exercise test, and angiographic features in predicting death, further ischaemic events, and left ventricular failure in a defined population from two adjacent health districts.

Patients and methods

Two centres contributed to this study—The London Hospital, Whitechapel, London E1 and Newham General Hospital, London E13.

Consecutive patients aged ≤65 who were clinically stable seven days after admission to hospital

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with a diagnosis of myocardial infarction were included in this study. Patients with haemodynamically important valve disease were excluded. For a diagnosis of myocardial infarction two out of the following three criteria had to be met: (*a*) typical cardiac pain lasting at least half an hour; (*b*) a typical rise in the enzymes aspartate aminotransferase and lactate dehydrogenase; (*c*) changes on consecutive resting electrocardiograms consistent with Q wave (>0·04 s duration and >25% of amplitude of subsequent R wave) or non-Q wave infarction; for a diagnosis of non-Q wave infarction, cardiac enzymes had to be raised to at least double the local laboratory upper limit of normal.

Changes in leads I, aVL, and V1–V4 were defined as anterior; changes in leads II, III, and aVF were defined as inferior; changes in V5 and V6 were defined as inferior if accompanied by changes in two out of the three leads II, III, and aVF, otherwise they were classified as anterior. Previous infarction was defined as a history of infarction supported by evidence from hospital notes of two of the above factors, or the presence of Q waves on the initial electrocardiogram in a territory showing no evolving changes.

STUDY GROUP

Three hundred and two consecutive, clinically stable, survivors of myocardial infarction (*group 1*) were identified. Table 1 gives the demographic details.

EXCLUSION GROUP

Fifteen patients were excluded because either they were unable to perform an exercise test or it would have been impossible to interpret the electrocardiograms (fig 1). These were (*a*) 10 with physical disabilities (three with severe chronic obstructive airways disease; five with severe locomotor problems; one with a disabling cerebrovascular accident after infarction; one with multiple systemic emboli after infarction), (*b*) four with left bundle branch block; and (*c*) one who developed unstable angina after the seventh day but before being able to perform an exercise test.

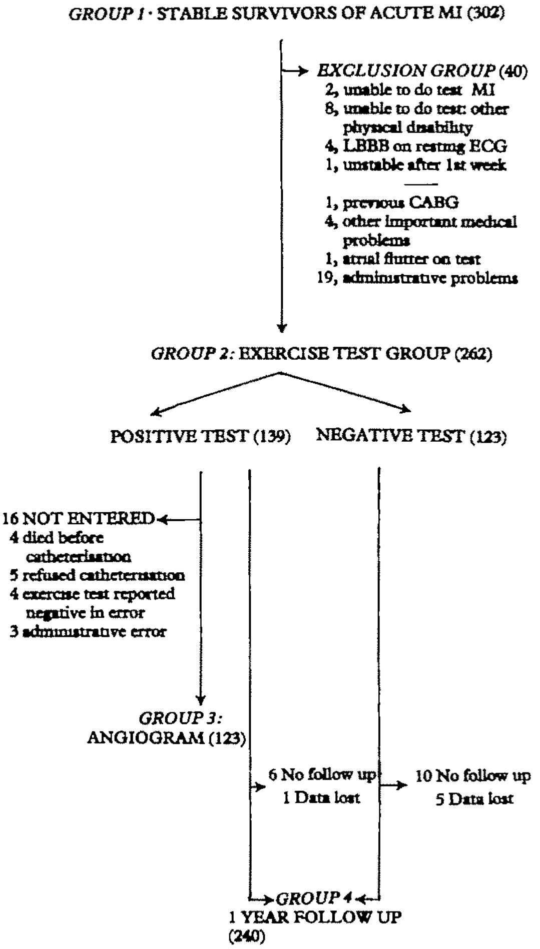

GROUP 1 · STABLE SURVIVORS OF ACUTE MI (302)
EXCLUSION GROUP (40)
2, unable to do test MI
8, unable to do test: other physical disability
4, LBBB on resting ECG
1, unstable after 1st week
1, previous CABG
4, other important medical problems
1, atrial flutter on test
19, administrative problems
GROUP 2: EXERCISE TEST GROUP (262)
POSITIVE TEST (139)
NEGATIVE TEST (123)
16 NOT ENTERED
4 died before catheterisation
5 refused catheterisation
4 exercise test reported negative in error
3 administrative error
GROUP 3: ANGIOGRAM (123)
6 No follow up
1 Data lost
10 No follow up
5 Data lost
GROUP 4
1 YEAR FOLLOW UP (240)

Fig 1 *Study outline. CABG, coronary artery bypass grafting; MI, myocardial infarction; ECG, electrocardiogram; LBBB, left bundle branch block.*

Twenty five other patients were not entered into the exercise test group: (*a*) one with previous coronary artery bypass grafting, (*b*) four with other significant medical conditions (two with severe alcohol-

Table 1 *Demographic data on study groups*

			Men		*Women*		*Asians*	
Group	*No*	*Mean age (SD)*	*No (%)*	*Mean age (SD)*	*No (%)*	*Mean age (SD)*	*No (%)*	*Mean age (SD)*
2 Stable survivors of MI	302	54 (7·3)	254 (84)	54 (7·4)	48 (16)	57 (5·5)	58 (20)	51 (6·7)
3 Patients with angiograms	123	54 (7·1)	104 (84)	53 (7·2)	20 (16)	56 (5·8)	16 (13)	50 (8 9)
4 Exercise test + follow up	240	54 (7 2)	206 (86)	53 (7 4)	34 (14)	56 (5 6)	42 (18)	50 (7 0)

MI, myocardial infarction.

ism; two with malignant disease); (*c*) one patient attempted an exercise test but it was stopped early because rapid atrial flutter developed; the inclusion protocol had not allowed for such a development; (*d*) 19 did not enter because of administrative problems.

EXERCISE TEST GROUP (GROUP 2)

This study therefore analyses the data from 262 patients, all of whom undertook an early submaximal exercise test. No β blockers had been prescribed for 36 hours and digoxin had been stopped at least seven days before the exercise test.

Exercise test protocol

Patients were exercised for the second and third stages of the modified Bruce protocol; the treadmill was set at a speed of 2·75 kph, and the gradients set for the two stages were 2·9° and 5·8° respectively. Three minutes' exercise was performed in each stage. Patients were tested a median of 11 days after infarction (interquartile range 9–12). Cuff systolic blood pressure measurements and a 12 lead electrocardiogram were recorded before the test with the patient standing upright on the treadmill; at the end of each 3 minute stage; and at the end of 2, 5, and 10 minutes of the recovery phase.

The test was stopped early if any of the following features developed: (*a*) severe angina pectoris; (*b*) severe dyspnoea, fatigue, or ataxia; (*c*) ST depression of ⩾ 5 mm, 80 ms after the J point; (*d*) 10 ventricular extrasystoles per minute or ventricular triplets.

A positive exercise test was defined as the development of (*a*) angina pectoris; (*b*) horizontal or downsloping ST depression ⩾1 mm, 80 ms after the J point; (*c*) an inappropriate blood pressure response defined as failure of the systolic blood pressure to rise 10 mm Hg or more, or, having risen, to fall again by 10 mm Hg or more (the latter finding had to be confirmed immediately the patient stopped exercising); (*d*) inability to complete the exercise test because of severe dyspnoea, fatigue, or ataxia; (*e*) increase in the frequency of ventricular extrasystoles of > 6 greater than the count on the pre-exercise electrocardiogram or development of ventricular triplets.

GROUP UNDERGOING CARDIAC CATHETERISATION (GROUP 3)

Cardiac catheterisation was performed at a median of 21 (interquartile range, 16–31) days after infarction in patients with a positive exercise test. One hundred and thirty nine patients (53% of group 2) were defined as having a positive exercise test but 16 of these patients did not undergo catheterisation for the following reasons: (*a*) four died before cardiac catheterisation; (*b*) five refused cardiac catheterisation; (*c*) four had exercise tests erroneously reported as "negative" (in each case an inappropriate blood pressure response had been overlooked) and were not therefore put forward for catheterisation; (*d*) three because of administrative error.

Study group 3 therefore consisted of 123 patients with a positive exercise test all of whom underwent cardiac catheterisation. Table 1 summarises their demographic data.

Follow up

The "positive" group were all prescribed a β blocker (sotalol), unless it was contraindicated, one to two days before discharge at a dose sufficient to reduce the resting heart rate to ⩽60. Patients with angina were treated with oral nitrates and calcium channel blockers and coronary artery bypass grafting was offered if they had angina resistant to medical treatment or left main stem stenosis or triple vessel disease with symptoms or exercise induced ST segment depression. Diuretics and vasodilators for heart failure were added as appropriate. Antiarrhythmic agents were given at the discretion of the physician under whose care the patient had originally been admitted. Treatment for the "negative" group was not standardised. Relevant follow up data were collected for one year after infarction.

Sixteen of the 262 patients in group 2 were lost to follow up (fig 1); six of these were from the "positive" exercise group and 10 were from the "negative" test

Site of infarction						
Anterior (%)		*Inferior (%)*				
Q (%)	*non-Q (%)*	*Q (%)*	*non-Q (%)*	*Both (%)*	*Unknown (%)*	*Prev MI (%)*
	143 (47)		141 (47)			
104 (73)	39 (27)	88 (62)	53 (38)	9 (3)	9 (3)	28 (9 3)
	54 (44)		66 (53)			
40 (74)	14 (26)	33 (50)	33 (50)	4 (3 2)	0 (0)	15 (12)
	116 (48)		115 (48)			
87 (75)	29 (25)	64 (56)	51 (44)	9 (3·8)	0 (0)	21 (8 8)

group. It was not possible to interpret the exercise tests of a further six patients because these tests were missing at the time of analysis, although they were recorded as being "negative" in five and "positive" in one. Follow up on these six was complete.

There were thus 240 patients with interpretable exercise tests with complete follow up (study *group 4*) (table 1). The data on these 240 patients were analysed and related to clinical outcome in the first year after infarction.

The study was approved by the ethics committees of both hospitals. All patients gave informed consent.

STATISTICAL ANALYSIS

Variables were entered into a data base on a Sperry PC/IT computer and analysed with the *SPSS/PC+* program. We used χ^2 analysis to compare groups defined by unordered categorical variables and Kendall's tau-C test for groups defined by ordered categorical variables. Means were compared by an analysis of variance method. Likelihood ratios were calculated where appropriate.[14] Certain variables, selected on the basis of the results of univariate analysis were used in log-linear analysis (SPCC/PC+ hiloglinear procedure). In each model, three variables were selected; those not contributing to prognosis were replaced until all variables had been included. A total of 60 variables were collected from which others were calculated; these described features of the history (demographic data, risk factors, and previous history), early 12 lead electrocardiogram, early (predischarge) clinical events, exercise test, angiograms, clinical follow up, and therapeutic manoeuvres. Collection of data was almost complete, but because this study was designed to study the power of an abnormal exercise test, we recorded the early clinical events only for patients with positive exercise tests. These data were also available for 17 of the 40 patients in the exclusion group, but they were not collected for patients with negative exercise tests. These clinical events included the following: ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia, or ventricular extrasystoles that required treatment) in the early ($\leqslant 72$ h) and late (> 72 h) period; left ventricular failure defined as a requirement for more than one dose of 40 mg frusemide; hypotension defined as a systolic blood pressure < 90 mm Hg; recurrent ischaemic pain > 48 h after infarction. Cardiac catheterisation provided several continuous variables. Two independent observers analysed the coronary arteriograms for the number of major vessels (left anterior descending, left circumflex, right coronary and the major intermediate artery) with a stenosis $> 50\%$. Figure 2 shows how the overall coronary artery score was derived. The left ventricular angiogram was assessed according to a wall motion score based on that used in Coronary Artery Surgery Study.[15] Collateral vessels to the infarct territory were scored as follows: 0, no collaterals; 1, faint blush of vessels only; 2, small collateral vessels easily seen, but insufficient to fill the epicardial portion of the infarct related artery; 3, collaterals easily seen, but only faintly filling the epicardial portion of the infarct related artery; 4, collaterals easily seen and fully filling the epicardial part of the infarct related artery.

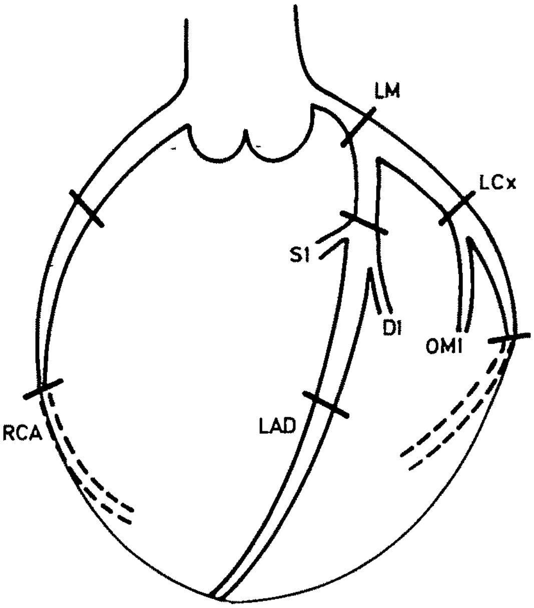


Fig 2 *Coronary artery scoring system. Diagram of the left anterior oblique view of coronary arteries as seen at angiography. LM, left main stem; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary; D1, first diagonal branch; S1, first septal branch; OM1, first obtuse marginal branch.*

The analysis was based on four major vessels (left anterior descending, left circumflex, right coronary, and the major intermediate (larger of major diagonal and obtuse marginal)) and the left main stem
Each major vessel (except left main stem) has three segments—proximal, middle, and distal. Each segment was given a score for.

Degree of stenosis	*Score*	*Score for proximal segment/left main stem*
0%	0	0
0–25%	1	2
25–50%	2	4
50–75%	3	6
75–99% (sub-total occlusion)	4	8
100% (total occlusion)	8	10

Only positive findings and relevant associations are reported in detail.

Results

ANALYSIS OF DEMOGRAPHIC DATA

Differences between patient groups

Table 1 shows that there were no important differences in the distribution of age and sex between the groups. The data were analysed to investigate the characteristics of patients who did not undergo an exercise test or cardiac catheterisation or who were lost to follow up.

Those who did not perform an exercise test (group 1 v group 2)—The 40 patients who did not perform an exercise test (the exclusion group (fig 1)) had a higher mortality (19 *v* 6·1%, p = 0·002), a higher mean age (59 *v* 54, p = 0·0001), and were more likely to have had a previous infarction (22 *v* 8%, p = 0·01) and to be female (30 *v* 14%, p = 0·009). There was no difference in the distribution of risk factors, site or type of infarction, or race.

Those lost to follow up (group 1 v group 4)—More Asian patients (19 *v* 6·9% of non-Asians, p = 0·005) and more diabetic patients (19 *v* 7 2% of non-diabetics, p = 0·03) were lost to follow up but there were no differences in age, sex, site or type of infarction, history of previous infarction, or other risk factors between those who were lost to follow up and those who were not.

Those who did not undergo cardiac catheterisation—Sixteen patients had a positive exercise test but did not undergo cardiac catheterisation ("Not entered", fig 1). The mortality of this group was significantly greater than that of the patients who had catheterisation (25 *v* 8·4%, p = 0·02). There were no other significant differences between these two groups.

INTERRELATIONS OF THE VARIABLES

To assess the predictive value of different variables derived from clinical data, exercise testing, and angiography, we analysed the pre-existing relations between the individual variables within these categories. Risk factor data were available for 260 patients, and early 12 lead electrocardiograms were available for 266 patients. Because the early clinical events were not recorded for the patients with negative exercise tests, there were only 155 patients with these variables recorded (132 of the 139 with positive exercise tests and all except 17 of the 40 patients in the exclusion group); exercise test variables for group 4 were virtually complete for all 240 patients; angiographic variables were available for all 123 patients undergoing the test, but in one patient left ventricular angiography was not performed because the procedure was stopped after arteriography.

Risk factor analysis (Group 1)

Risk factor data were available in all but seven of the 302 patients in group 1; of the remaining 295, 238 (81%) were smokers, 67 (23%) had a positive family history, 48 (16%) gave a history of previously diagnosed hypertension, 32 (11%) had previously had diabetes diagnosed, five (1·7%) had gout, and only one (0·3%) gave a history of hyperlipidaemia. Thirty five (12%) had no risk factors.

Interrelations of data acquired from the history (from group 1) (table 1)

The mean age for men was significantly lower than that for women (p = 0·005), and that of the Asian men was significantly lower than that of the non-Asian men (p = 0·0003). The mean age of those who gave a history of previous infarction was not significantly higher than that of those with first infarcts. More women than men had a positive family history (37 *v* 20%, p = 0·01), and more had had hypertension diagnosed (26 *v* 14%, p = 0·05). More diabetic patients than non-diabetic patients were known to have hypertension (31 *v* 14%, p = 0·02). Although proportionately more of the diabetic patients were non-smokers than the non-diabetic patients (31 *v* 18%), this difference was not statistically significant. A higher percentage of diabetic patients had electrocardiographic evidence of infarction in both anterior and inferior territories but the difference between the diabetic and non-diabetic patients was not significant.

Interrelations of early clinical events

Among the patients for whom these data were available (a relatively high risk group), only two significant associations were found: (*a*) three (16%) of the 19 patients in whom angina developed >48 h after onset of the chest pain that prompted admission to hospital had late (>72 hours after infarction) ventricular arrhythmias compared with three (2%) of 151 patients without such angina (p = 0·02); (*b*) three (9·7%) of 31 patients in whom early left ventricular failure developed also had early (⩽72 hours) ventricular arrhythmias compared with one (0·7%) of 139 patients without failure (p = 0·02).

Interrelations of exercise test variables (table 2)

There were very strong interrelations between the development of ST depression, angina, and an abnormal blood pressure response; ST depression in the non-infarct zone of the electrocardiogram was also associated with ST elevation in leads showing Q wave infarction. There was also a very strong association between the development of angina and both an abnormal blood pressure response and an inability to complete the exercise protocol. There were weaker but significant associations between an abnormal blood pressure response and an inability to complete

Table 2 *Interrelations of exercise test variables*

Feature	*No cases*	*Angina (%)*	*Abnormal BP response (%)*	*Inability to complete test (%)*	*VA (%)*	*ST elevation (%)*
ST depression:						
Present	104	37 (36)	26 (25)	11 (11)	7 (6·7)	40 (38)
Absent	146	15 (10)	18 (12)	10 (6·9)	8 (5·5)	36 (25)
p		0 0001	0 006	0 3	0 7	0 02
Angina:						
Present	52	—	20 (38)	10 (20)	5 (9 6)	18 (35)
Absent	198	—	24 (12)	11 (5·6)	10 (5 1)	58 (29)
p			0·0001	0·001	0·22	0·5
Abnormal BP response:						
Present	44	—	—	8 (18)	4 (9 3)	18 (41)
Absent	206	—	—	13 (6·3)	11 (5·3)	58 (28)
p				0 01	0 3	0 1
Inability to complete:						
Present	20	—	—	—	1 (5)	8 (38)
Absent	228	—	—	—	13 (5 7)	68 (30)
p					0·9	0 4
Ventricular arrhythmias:						
Present	15	—	—	—	—	9 (60)
Absent	234	—	—	—	—	67 (29)
p						0 01

Only cases for which all the data were available were analysed.
p values are significance levels for χ^2 tests before Yates' correction.
BP, blood pressure; VA, ventricular arrhythmia.

the test, and also between the development of a ventricular rhythm disturbance and the development of ST elevation.

Interrelations of angiographic variables (table 3)

There was no interrelation between the left ventricular and coronary artery scores nor between the left ventricular and collateral scores. There was, however, a highly significant association between the coronary artery and collateral scores. The group of patients with high coronary artery scores ($\geqslant 19$, see below) were nearly three times more likely to have obvious collaterals (scores 3 and 4) than the group with low coronary artery scores.

Interrelations of end points

The clinical outcomes, that is cardiac death, an "ischaemic" end point (development of angina, further infarction, or requirement for operation), and the development of overt left ventricular failure were analysed by the hiloglinear procedure. There were no associations between these end points other than a non-significant relation between the development of overt left ventricular failure and mortality. Fourteen of the patients who underwent an exercise test died in the first year; 10 died suddenly (one each at 10, 11, and 14 days after infarction, one at two months, three at three months, and one each at five, seven, and nine months after infarction). Two of them had ventricular fibrillation; two died within an hour of complaining of chest pain; two patients died after confirmed recurrent myocardial infarction; one died in congestive heart failure at two months; one died of unknown cause at one month. The "ischaemic" end points were interrelated. Thirty (27%) of the 113 patients who developed angina in the first year after discharge underwent coronary surgery compared with two (1·3%) of 157 patients who did not complain of angina ($p < 0·0001$); the development of further infarction, however, was unrelated to the development of angina or the need for operation.

SAFETY OF EARLY SUBMAXIMAL EXERCISE TEST

There was no mortality and no major complication

Table 3 *Relation of collateral score to left ventricular (LV) and coronary artery (CA) scores*

Collateral score	*CA score ≥19*	*CA score <19*	*Likelihood ratio**	*Relative odds*	*LV score ≥21*	*LV score <21*	*Likelihood ratio**	*Relative odds*
4	39	15	2 2	2·9	25	28	0 84	1·0
3	11	13	1·5		12	12	0·87	
2	4	6	1·3	1·0	3	7	0·80	1·5
1	3	6	1·2		9	0	0·98	
0	10	16	1·0		14	12	1·0	

*For cut off point, not for individual collateral score.

Table 4 *Discriminatory power of the "positive" submaximal exercise test*

Exercise test result	*No cases*	*Deaths*	*Relative odds*	*"Ischaemic event"*	*Relative odds*	*LVF*	*Relative odds*	*Well (none of these)*	*Relative odds*
With our predetermined criteria for positivity									
Positive	133	14	13	76	2·8	8	2·3	35	1
Negative	113	1	1	34	1	3	1	75	5·5
With ST elevation in the infarct territory added as an additional feature for positivity									
Positive	153	15	∞	80	2·3	9	2·8	49	1
Negative	93	0	—	30	1	2	1	61	4·0

LVF, left ventricular failure.

from the early submaximal exercise test. In four patients well tolerated ventricular tachycardia developed; one required a precordial thump to restore sinus rhythm; the others had short lived, self terminating events.

DISCRIMINATORY POWER OF THE "POSITIVE" EXERCISE TEST (TABLE 4)

A patient with a positive test was 13 times more likely to die in the year after infarction than a patient with a negative exercise test. A patient with a positive test was nearly three times more likely to have a further infarct, develop angina, or require coronary artery bypass grafting than a patient with a negative test. In addition, those patients with a positive exercise test were more than twice as likely to develop overt left ventricular failure in the first year after infarction.

The data were re-analysed to investigate whether the addition of ST elevation as a positive feature improved the discriminatory power of the exercise test. The prediction of death and overt left ventricular failure was improved, but the test became a weaker predictor of further ischaemic events. The predictive accuracy of a negative test for a good outcome was weakened by the inclusion of ST elevation.

PROGNOSTIC POWER OF VARIABLES

Predictors of mortality (table 5)

Univariate analysis—Table 5 shows the features of the history, early 12 lead electrocardiogram, early clinical events, exercise test, and angiogram that were predictive of mortality and the relative odds for mortality associated with these variables. The mean left ventricular score of those who died was significantly higher than that of survivors. Patients with a left ventricular score of $\geqslant 30$, for example, were six times more likely to die than the rest of the group (see fig 3a). Patients with a left ventricular score of $\geqslant 21$ were twice as likely to die than those with a lower score. The coronary artery score on the other hand was not a predictor of death in the first year after infarction (see fig 4b), nor was the collateral score related to mortality.

Multivariable analysis—*(a)* **Features of history and early 12 lead electrocardiogram.** A history of previous infarction was the only powerful predictor of mortality in the first year ($p = 0{\cdot}003$) and a history of diabetes added some additional prognostic information ($p = 0{\cdot}05$). The other variables did not remain independent predictors. (*b*) **Features of exercise test alone and together with clinical variables.** For the whole group the development of ventricular arrhythmias was the most powerful predictor of mortality from the exercise test ($p = 0{\cdot}007$), although a blood pressure of $\leqslant 100$ mm Hg at the beginning of the exercise test ($p = 0{\cdot}03$) and inability to complete the test ($p = 0{\cdot}04$) were also independent markers for this end point. For the subgroup of patients who completed six minutes of exercise, a blood pressure of $\leqslant 130$ mm Hg at the end of exercise was the only predictor of mortality ($p = 0{\cdot}02$). Analysis of these variables together with the features from the history, electrocardiogram, and early clinical events showed that for the whole group the development of ventricular arrhythmias on the exercise test ($p = 0{\cdot}02$) and the development of ventricular arrhythmias >72 hours after infarction ($p = 0{\cdot}03$) were independent markers for mortality. (*c*) **All features, including angiographic variables.** A left ventricular score $\geqslant 21$ was added to the previous variables from the history and exercise test. Both a high left ventricular score ($p = 0{\cdot}0003$) and ventricular arrhythmias occurring >72 hours after infarction ($p = 0{\cdot}04$) were independent predictors of mortality in this group of patients.

PREDICTORS OF "ISCHAEMIC" END POINTS

The development of angina pectoris, further infarction, or a requirement for coronary artery bypass grafting in the first year after infarction were all regarded as ischaemic end points.

Univariate analysis

Table 5 shows the variables identified as predictors of an ischaemic end point and their associated relative odds. The coronary artery score was predictive of the development of an ischaemic end point; those with a score >30 were over three and a half times more

Table 5 *Predictors of clinical end points (univariate analysis)*

Predictors of mortality				*Predictors of ischaemic events*				*Predictors of left ventricular failure (LVF)*			
Feature	*Cases*	*Deaths*	*Relative odds*	*Feature*	*Cases*	*Events*	*Relative odds*	*Feature*	*Cases*	*LVF*	*Relative odds*
				History/electrocardiogram							
Previous MI:				No risk factors:				Previous MI:			
Yes	25	6	5·7	4	3	2	4 4	Yes	25	4	9·2
No	245	13	1	3	21	14	4·4	No	245	5	1
Site of MI:				2	71	34	2				
Ant + Inf	9	1	2·5	1	143	64	1·8				
Anterior	130	12	2	0	32	10	1				
Inferior	127	6	1	Previous MI:							
Diabetes:				Yes	25	17	2·7				
Yes	26	4	2·6	No	245	107	1				
No	244	15	1	Non-Q MI:							
Hypertension:				Non-Q	88	53	2 4				
Yes	45	5	1·9	Q	178	69	1				
No	225	14	1	Diabetes:							
				Yes	26	15	1 7				
				No	244	109	1				
				*Early clinical events**							
Late ventricular arrhythmia:				Early angina:							
Yes	6	3	10 4	Yes	19	17	7·3				
No	149	13	1	No	136	73	1				
				Exercise test							
Ventricular arrhythmia:				Angina:				Inability to complete:			
Yes	15	4	7	Yes	52	39	5·6	Unable	17	4	7 1
No	224	11	1	No	188	70	1	Able	218	7	1
Abnormal BP:				Inability to complete:				Pre-test heart rate ≥ 100 beats/min			
Yes	43	6	3 4	Unable	17	16	4·3	Yes	27	4	5 1
No	197	9	1	Able	218	93	1	No	212	7	1
Pre-test BP ≤ 100 mm Hg:				ST depression:				Pre-test double product ≥ 10000·			
Yes	39	5	2·8	Yes	101	58	2 3	Yes	85	8	5 2
No	200	10	1	No	139	51	1	No	154	3	1
BP ≤ 130 mm Hg at 6 min.								Heart rate at 6 min ≥ 140 beats/min:			
Yes	81	7	3 1					Yes	34	5	15 6
No	136	4	1					No	183	2	1

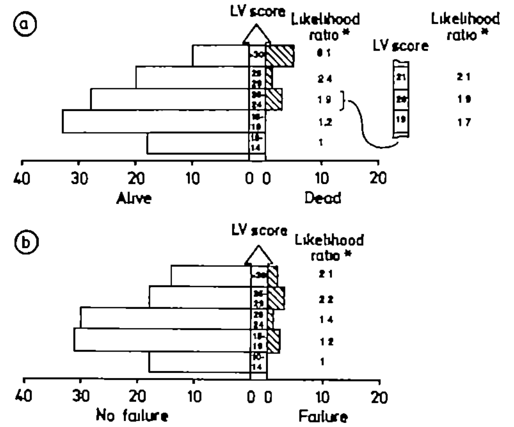
				Angiogram†							
Outcome	*No*	*Mean score (SD)*	*p*	*Outcome*	*No*	*Mean score (SD)*	*p*	*Outcome*	*No*	*Mean score (SD)*	*p*
LV score.											
Dead	9	28 (5 4)	0 0004	Event	75	21 (6·5)	NS	LVF	8	25 (6·3)	NS
Alive	109	21 (6·1)		None	43	21 (6·1)		No LVF	110	21 (6·3)	
CA score:											
Dead	10	24 (8 8)	NS	Event	75	23 (8·5)	0 0004	LVF	8	23 (9·9)	NS
Alive	109	21 (8 3)		None	44	18 (6 9)		No LVF	111	21 (8·3)	
Collateral score:											
Dead	10	2·1 (1 7)	NS	Event	75	2·5 (1 7)	NS	LVF	8	2·1 (1·6)	NS
Alive	109	2 7 (1·6)		None	44	2 7 (1 4)		No LVF	111	2 6 (1·6)	

*Not recorded for patients with negative exercise tests; late ventricular arrhythmias occurred > 72 h after infarction but before discharge; early angina occurred > 48 h after infarction but before discharge.
†One patient had coronary arteriography but not left ventricular angiography.
LVF, left ventricular failure; BP, blood pressure; LV, left ventricular; CA, coronary artery; MI, myocardial infarction.

likely to have such an end point than those with a lower score (fig 4a); the chances of such an end point were doubled with a coronary score of ≥ 19. The left ventricular and collateral scores did not contribute to the prediction of these end points.

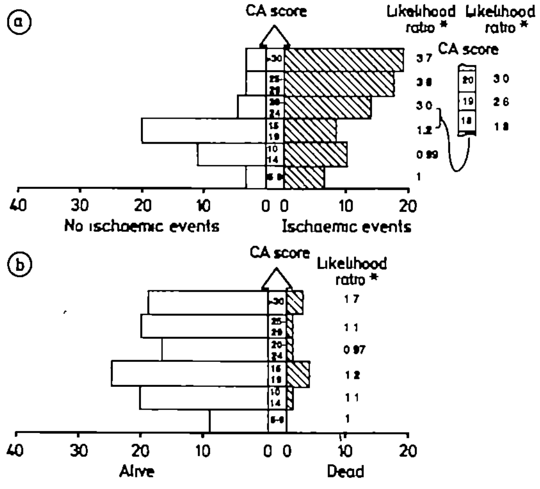
Multivariable analysis—(a) **Features of history and early 12 lead electrocardiogram.** The most powerful predictor of ischaemic end points was the presence of non-Q wave infarction ($p = 0{\cdot}0009$); a history of previous infarction ($p = 0{\cdot}02$) and having more than two risk factors ($p = 0{\cdot}03$) were also independently predictive of further ischaemic events. (b) **Features of exercise test alone and together with clinical variables.** Of the exercise test variables the development of angina on the exercise test was the most powerful predictor of an ischaemic event in the subsequent year ($p = 0{\cdot}0001$). Although there are strong associations between the development of angina, ST segment depression, and an inability to complete the test (table 2), an inability to complete the test was also an independent predictor of future ischaemic events ($p = 0{\cdot}03$).

Analysis of the exercise test variables together with



*For cut-off, not for individual LV score group

Fig 3 *Left ventricular (LV) score as (a) a predictor of mortality and (b) of clinical left ventricular failure. Likelihood ratios are calculated by comparing the number of end points in patients with all scores above the lower value for each subgroup with those with all scores lower than this value. The score at which the likelihood of an end point is doubled is shown.*



*For cut-off, not for individual LV score group

Fig 4 *Coronary artery (CA) score as (a) a predictor of further ischaemic events but (b) not for mortality. See legend to fig 3 for explanation of likelihood ratios.*

the features of the history, electrocardiogram, and early clinical events, showed that angina on the exercise test (p = 0·001), the development of angina >48 hours after infarction (p = 0·001), and the presence of non-Q wave infarction (p = 0·04) were independent predictors. Repeat analysis for the separate ischaemic components showed that the development of angina on the exercise test (p = 0·0005), angina >48 hours after infarction (p = 0·002), and non-Q wave infarction (p = 0·008) were independent predictors of the development of angina in the first year after discharge. These three variables were also independently predictive of the need for operation (p = 0·003, p = 0·008, and p = 0·001 respectively). The only predictor of further infarction was the presence of non-Q wave infarction (p = 0·009). (c) **All features, including angiographic variables.** A high coronary artery score (≥19) (p < 0·0001), the development of angina on the exercise test (p = 0·0008), and early angina (p = 0·01) were independent predictors of these end points. Analysis for the separate components of this group of end points showed that these variables were independent predictors of angina in the first year after discharge (p < 0·0001, p = 0·0001, and p = 0·03 respectively); the need for operation was predicted independently by a high coronary score (p < 0·0001), non-Q wave infarction (p = 0·001), and early angina (p = 0·003); non-Q wave infarction was the only predictor for myocardial infarction (p = 0·01).

PREDICTORS OF THE DEVELOPMENT OF LEFT VENTRICULAR FAILURE

Univariate analysis

Table 5 shows the variables that predicted this end point together with their associated relative risks. The mean left ventricular score of those who later developed left ventricular failure was higher than that of the patients who did not, but this difference did not reach statistical significance. More detailed analysis showed that patients with a score ≥25 or more were twice as likely to develop failure as those with a lower score (fig 3b). The coronary artery score was not predictive for this outcome nor was the collateral score.

Multivariable analysis

Because a history of previous infarction was the only predictor of this end point, multivariable analysis was not performed on the variables of the history and 12 lead electrocardiogram alone. (a) **Features of the exercise test alone and together with clinical variables.** From the exercise test an inability to complete the exercise test (p = 0·04) and a double product of ≥10 000 at rest (p = 0·04) were both independent predictors for the development of overt left ventricular failure in the year after discharge. For the subgroup of patients who completed the test a heart rate of ≥140 beats per minute at six minutes exercise was a powerful predictor of later heart failure (p = 0·0007), with other features adding no further prognostic information. The exercise test variables were then analysed with the other features, but as none of the early clinical events was predictive of this end point, they were not included in this analysis. The exercise test variables remained independently predictive, but a history of previous infarction did not. (b) **All features including angiographic variables.** The only independent predictor for left ventricular failure was a double product of ≥10 000 at the start of the exercise test (p = 0·001). For the subgroup of patients who completed six minutes' exercise the only predictor was a heart rate of ≥140 beats/min at the end of exercise (p = 0·01).

Discussion

Exercise testing is a useful prognostic indicator in patients after myocardial infarction.[1-4 16-19] Undue emphasis should not be placed on one investigation, without consideration of its value in relation to other clinical data. Univariate analysis of diagnostic features that predict an outcome does not take into account their interrelations with other variables. Multivariable analysis gives results that are more valuable in clinical practice because this method identifies those clinical features that are the most useful predictors of outcome. In addition, the use of likelihood ratios provides a more meaningful analysis for the clinician than a list of significance values for each variable.[14]

It is important to define the population that has been investigated in a clinical study. We investigated consecutive survivors of myocardial infarction who were clinically stable seven days after admission to hospital. The demographic details of our patient group differ from other studies of men[2 20] or non-consecutive patients.[20 21] We set out to evaluate the contribution of the exercise test in identifying high risk groups among clinically stable survivors of infarction. The exclusion criteria mean that 13% of the patients did not perform an exercise test. As with other studies,[4 17 18] the mortality of this exclusion group was higher than that in the exercise test group (19% in the first year compared with 6%). This was expected because the excluded group contained patients with high risk factors and other important medical conditions.

An early submaximal treadmill exercise test was performed by 87% of all the clinically stable survivors we identified. We had hoped to include all patients fitting the entry criteria for the study protocol, but further analysis of the exclusion group showed that a disproportionate number of women did not perform the exercise test; this may be because the general physicians under whose care they had been admitted tended to treat women more conservatively. The exclusion group was significantly older than those who exercised; this is partly because older patients were more likely to have other midical conditions that prevent them from performing the test.

In some reports the study group contained proportionately more patients with inferior infarction,[2 18 20] because of the exclusion or selection criteria. It becomes difficult under these circumstances to extrapolate to all survivors of infarction. In our study there were equal numbers of patients with anterior and inferior infarcts in the group that performed an exercise test. Exclusion of patients with heart failure[2 20 22] early after infarction may select out patients with large anterior infarcts and this limits the value of the exercise test in predicting late complications.

The analysis of risk factors in this study emphasises the association between smoking and myocardial infarction.[23] Analysis of the interrelations between risk factors and other demographic data showed some interesting associations. Women were older and more likely to have a family history of coronary disease and a history of hypertension than men. Multiple risk factors were shown to have an additive effect in the prediction of future ischaemic events. Analysis of the demographic data also showed that Asians and diabetic patients were more likely to be lost to follow up.

Use of a predischarge submaximal exercise test to distinguish high and low risk groups[7] is a compromise between a maximal exercise test protocol,[2 16 24-26] and a delayed exercise test performed six weeks or more after infarction, which may miss those at highest risk of early clinical events.[16 27] The early submaximal exercise test was found to be safe and to have powerful discriminating power; all clinical end points were more common in those with a positive test than those with a negative test. Those with a positive test were 13 times more likely to die in the first year after infarction. The low mortality of the group with negative exercise tests supports a policy restricting the use of angiography to those with a positive exercise test.

Multivariable analysis showed that ventricular arrhythmias occurring >72 hours after infarction but before discharge and during the exercise test were independent predictors of mortality, but when the angiography was added to the analysis the extent of left ventricular damage replaced exercise induced arrhythmias as an independent marker for this end point. Similarly, angina (early) after infarction, angina occurring during the exercise test, and the prescence of non-Q wave infarction were independent predictors of all ischaemic end points in the first year after discharge. When angiographic variables were added to the analysis, however, the extent of coronary disease replaced non-Q wave infarction as an independent predictor. Sub-analysis for the separate ischaemic end points showed that the extent of coronary disease and angina occurring early and during exercise predicted the development of angina later in the year. The need for operation was predicted independently by the extent of coronary disease, the development of early angina, and non-Q wave infarction but not independently by the development of angina during the exercise test. Of all these variables, only non-Q wave infarction predicted further infarction. A double product ≥10 000 before exercise testing was the only independent predictor of future left ventricular failure. When a left ventricular score ≥ 21 was considered this gave no additional prognostic information, but the likelihood of this event was related to the extent of ventricular damage. A score of 21 was selected because it was not only the mean for the group who had angiography but it was also the level at which the odds of dying were doubled by a high score (≥21).

The criteria used to define a positive exercise test have thus been confirmed as being useful markers for clinical end points. We did not include ST elevation in the infarct zone of the electrocardiogram as a criterion for a positive exercise test. Because some patients with this feature went into the negative group and thus did not undergo cardiac catheterisation, we can draw no conclusions on the relative values of this criterion and the variables generated by angiography. Although in this study it was not itself predictive of first year mortality, there was an association between ST elevation and the development of ventricular arrhythmias on the exercise test and we have data (not yet published) to support other groups' findings that it is associated with the extent of left ventricular damage.[21 28 29] When the discriminatory power of a positive exercise test was reanalysed with ST elevation included as a feature, the test became 100% sensitive in predicting mortality, although it was less specific.

Conclusions about outcome established by the analysis of this study group reflect the natural history after infarction as modified by current treatment. It was intended that all patients with a positive exercise test should receive a β blocker; not all patients could tolerate this treatment, either because of poor left ventricular function or chronic obstructive airways disease. Antianginal treatment (whether medical or surgical), treatment for heart failure, and antiarrhythmic treatment were added as appropriate. Those with negative exercise tests were managed at the discretion of their referring physicians; not all received a β blocker and despite a lack of standardised management, the one year mortality in this group was small (one of 113 patients with complete follow up, 0·9%, 95% confidence interval 0·02–4·6%).

The early clinical features available to the physician (including features of the chest radiograph and electrocardiogram) have been used in several risk stratification scores.[30 31] We studied patients who were haemodynamically stable and who were about to go home after infarction. We attempted to consider not only their overall risk for dying, but also the variables that are able to predict specific end points that might have been avoided by specific treatments. We do not propose that submaximal exercise testing should replace previous stratification scores, but rather than they should supplement them when haemodynamically stable patients are about to be discharged home.

Risk stratification after infarction permits the identification of low risk patients who can be reassured, need few follow up examinations, and may not need secondary preventive medication. Appropriate treatment resources can then be concentrated on the high risk groups. The early development of clinical events (such as cardiogenic shock or continuing ischaemic pain) will identify one high risk group. For those being discharged from hospital, it has been established that the use of β blockers improves the chance of survival in the first year after infarction[32]; however, patients with poor left ventricular function may not tolerate these drugs. This study showed that despite their use (and that of other standard treatments such as coronary artery surgery and antiarrhythmic agents), high risk groups are still discernible. Coronary artery bypass grafting improves prognosis for patients with certain arteriographic patterns of disease,[33-35] and it is probable that this is valid for patients after infarction.[36] Studies need to be conducted to establish whether the benefits of other specific treatment regimens outweighs their hazards, and those patients most likely to be helped must be identified. A protocol that used submaximal exercise testing followed by left ventricular and coronary angiography in selected patients provides a powerful means of identifying those at risk of future clinical events, as long as the relative predictive powers of the many variables provided are appreciated.

This paper shows that an early submaximal exercise test safely identifies groups at high risk of several outcomes. Patients who are not exercised constitute a high risk group for the reasons discussed. Patients with a negative exercise test have a very low mortality. For patients with a positive test, the use of multivariable analysis shows the relative power of one variable in relation to other clinical and angiographic variables. Not only is prediction better than clinical and electrocardiographic variables aloned, but the selection of patients with a positive test for cardiac catheterisation further refines risk stratification and identifies patients who are more likely to benefit from early operation. Further studies are required to investigate the role of specific treatments in those identified to be at highest risk of certain clinical outcomes.

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Diabetes, hyperinsulinaemia, and coronary risk factors in Bangladeshis in East London

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SUMMARY Immigrants from the Indian subcontinent (South Asians) in England and Wales have higher morbidity and mortality from coronary heart disease than the general population; this seems to apply to both Hindus and Muslims. Studies in north west London and Trinidad found that the increased risk of coronary heart disease in Indians was not explained by dietary fat intakes, smoking, blood pressure, or plasma lipids. In the present study the distribution of coronary risk factors was measured in an East London borough where the mortality and attack rate from coronary heart disease are higher in the Asian population, predominantly Muslims from Bangladesh, than in the rest of the population. In a sample of 253 men and women aged 35–69 from general practice, mean plasma cholesterol concentrations were lower in Bangladeshi than in European men and women. Mean systolic blood pressures were 10 mm Hg lower in Bangladeshis. Plasma fibrinogen concentrations were similar in Bangladeshis and Europeans and factor VII coagulant activity was lower in Bangladeshi than in European men. In contrast with the findings in Hindus in north west London, smoking rates were high in Bangladeshi men and the ratio of polyunsaturated fatty acids to saturated fatty acids in plasma lipids was lower in Bangladeshis than in Europeans. Diabetes was three times more common in Bangladeshis than in Europeans and serum insulin concentrations measured after a glucose load were twice as high in Bangladeshis. High insulin concentrations in Bangladeshis were associated with high plasma triglyceride and low high-density lipoprotein cholesterol concentrations.

Insulin resistance, leading to diabetes, hyperinsulinaemia, and secondary lipoprotein disturbances, is a possible mechanism for the high rates of coronary heart disease in South Asians in Britain and overseas.

Death rates from coronary heart disease in men and women born in the Indian subcontinent (South Asians) who live in England and Wales are higher than in the general population, and this high rate is shared by Gujaratis, Punjabis, South Indians, and Muslims.[1 2] Similar findings have been reported for other Indian populations overseas.[3] In a survey in the north west London boroughs of Brent and Harrow we found that South Asians had lower dietary intakes of saturated fat and cholesterol, higher ratios of dietary polyunsaturated to saturated fat, lower concentrations of plasma cholesterol, and smoked less than the average for the British population.[4] These findings were confirmed in Brent by other investigators[5] and yet the standardised mortality ratio for coronary heart disease for those born in the Indian subcontinent or East Africa who were resident in Brent or Harrow in 1979–83 was 163 for men and 157 for women.

This study of a Gujarati Hindu population provided no clues to the reasons for the increase in coronary heart disease, and the results did not accord with current thinking on the causes of coronary heart disease. This prompted us to study Muslims from the Sylhet region of Bangladesh who have settled in the East London borough of Tower Hamlets. In 1970–72 Bangladeshi men in this district were first reported to have a higher morbidity from coronary heart dis-

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ease.[6] The objectives of our study were to determine whether the findings in north west London could be replicated in a Muslim population from the Indian subcontinent and secondly to investigate whether the increases in coronary heart disease in immigrants from the Indian subcontinent in Britain can be explained by other risk factors that were not measured in the earlier study, such as hypertension, increased haemostatic activity, and glucose intolerance.

Methods

SAMPLING

From published reports we estimated the size of difference in the distribution of each risk factor that would give rise to a 20% difference between two populations in coronary heart disease mortality in men. A target sample size sufficient to detect such differences was estimated to be about 80 men in each ethnic group. We obtained approval for the study from local ethics committees.

Fieldwork was undertaken between June 1985 and April 1986. The study area was defined as postal districts E1 and E2—the western half of the borough of Tower Hamlets. Most of the borough's Bangladeshi residents live in this area and are registered with one of three local practices. The lists of these three practices and of a further two practices with mostly native British patients were chosen as the sampling frame. A sample of men born between 1920 and 1949 was chosen from each practice, excluding residents in hostels for the single homeless and those with mental handicap, recent psychiatric illness, terminal malignancy, or other advanced disease. To minimise the proportion of wrong addresses, those who had not consulted their doctor since 1981 or who last attended for immunisation before returning to Bangladesh were also excluded because they were unlikely to be still resident. The proportions sampled from each practice were adjusted to ensure approximately equal numbers of Bangladeshi and control respondents. In three practices which had age-sex registers the sample was stratified by year of birth to give an even distribution across the age range. In the early stages of the study, women aged over 35 years who were married to Bangladeshi respondents were also invited to take part: because of the age difference between husbands and wives this proved to be an unsatisfactory means of sampling older Bangladeshi women. A sample of women was chosen independently from four of the practices in the last four months of fieldwork. In one practice whose list was made up predominantly of Bangladeshi residents, only women born before 1940 were included at this stage. Apart from the exclusions and the stratification by age, sex, and practice, the sampling procedure was random.

Each eligible person was sent a letter inviting them to participate. We visited addresses from which no reply was received to ascertain whether the address was correct and to issue a further invitation. Of the 557 people to whom letters were sent, 173 had moved to other addresses either outside the district or unknown, two had died, and one was in hospital. Of the 381 remaining, 58 refused, three were medically unfit to take part, and it was not possible to contact 12. Three hundred and eight interviews were completed—a response rate of 81% from those believed to be resident.

Respondents were interviewed at home with a questionnaire including demographic items, smoking, alcohol consumption, and medical history, and invited to attend the London Hospital Medical College for measurement of blood pressure and blood sampling. Most Bangladeshis were interviewed in Bengali (by SR) and most Europeans in English (by DEC or PMM). Those without a history of diabetes were asked to fast overnight and consume a 75 g glucose drink an hour and a half before their appointment. Two hundred and fifty three participants attended for examination, giving a final response rate of 66%. The target sample size was reached for men but not for women. Table 1 shows the age distribution of the respondents. There were few Bangladeshi women who were younger than 45 or older than 54. This was a result of the unusual demographic structure of the population and the restriction of the Bangladeshi sample to women born before 1940 in the later stages of the fieldwork. Blood pressure was measured twice with a random zero sphygmomanometer after the subject had been sitting quietly for five minutes: all measurements were made by one observer (PMM). A single venous sample was obtained from 247 of the 253 attenders: in those who had been given a glucose load this was taken as close as possible to two hours after the reported time of consumption.

LABORATORY ANALYSES

Plasma treated with edetic acid was kept at 4°C for up to 48 hours before analysis. High density lipoprotein

Table 1 *Numbers attending field station by age, sex, and ethnic category*

Age (yr)	*Men*		*Women*	
	Bangladeshi	*Non-Asian*	*Bangladeshi*	*Non-Asian*
35–44	17	22	3	12
45–54	35	35	38	11
55–64	22	31	4	18
65–69	2	2		1
All	76	90	45	42

was separated by precipitation with heparin-manganese chloride; cholesterol in these specimens and in whole plasma was measured enzymatically in a centrifugal analyser. The concentration of plasma glucose was measured on a fluoride oxalate specimen by the glucose oxidase method. Fibrinogen concentrations in fresh citrated plasma were measured by a gravimetric method.[7] Citrated plasma samples for factor VII determination were stored in liquid nitrogen, thawed at 37°C, and maintained at room temperature to avoid cold activation. We assayed factor VII coagulant activity by a manual method based on that of Brozovic *et al*[8] with immuno AG 100% reference plasma in doubling dilutions from 1/10 to 1/360, 0·025 mol/l calcium chloride, and 1 in 32 rabbit brain thromboplastin. Factor VII deficient plasma was prepared from oxalated bovine blood by a modification[8] of the method of Lechner and Deutsch.[9] We measured the fatty acid composition of plasma lipids of a random subsample of those seen in the last six months of fieldwork by a technique described previously.[4] Insulin concentrations in stored serum were measured by a double antibody technique.[10]

STATISTICAL ANALYSES

Mortality ratios for particular boroughs, expressed as percentages and determined for each sex separately, are based on population figures from the 1981 Census and on death records supplied by the Office of Population Censuses and Surveys. The standardised mortality ratio compares the observed number of deaths from coronary heart disease in Bangladeshis with the number that would be expected if the age specific mortality rates were the same in Bangladeshis as in all residents of the borough. The proportional mortality ratio compares the observed number of deaths from coronary heart disease in Bangladeshis with the number that would be expected if, in each age group, the proportion of deaths attributed to coronary heart disease were the same in Bangladeshis as in the general population of the borough. Unlike the standardised mortality ratio, the proportional mortality ratio does not depend on Census data and it measures the extent to which excess coronary mortality is cause specific.

All those of South Asian origin were included in the group referred to as Bangladeshi and all other subjects, including three Afro-Caribbeans, have been assigned to the non-Asian group: this is consistent with the grouping used in analyses of local morbidity and mortality. Participants were classified as diabetic if diabetes had been diagnosed or if their post-load plasma glucose was $\geqslant 11$ mmol/l. Known diabetic patients were excluded from the data for plasma insulin and triglycerides because they did not fast or receive a glucose load. To test for differences between ethnic groups we analysed data separately for men and women using a least squares linear model. Age was treated as a categoric variable with three levels corresponding to the age groups 35–44, 45–54, and 55–69 years. Adjusted means are the values predicted in the model when all covariates are held at their mean values. Other covariates—body mass index, triglycerides, and insulin—were treated as continuous variables. Triglyceride and insulin values were log transformed for these analyses but have been transformed back to SI units for the tabulations. In figs 1 and 2 data for women are given for only two age bands because of small numbers of Bangladeshi women at the extremes of the age range.

Results

QUESTIONNAIRES

Eighty nine per cent of Bangladeshi men and 80% of non-Asian men belonged to social classes III manual or IV by the Registrar General's classification.[11] Fifty three per cent of Bangladeshi men and 20% of non-Asian men were unemployed. Ninety seven per cent of Bangladeshis were Muslim and 91% were from Sylhet. Although most Bangladeshi men were

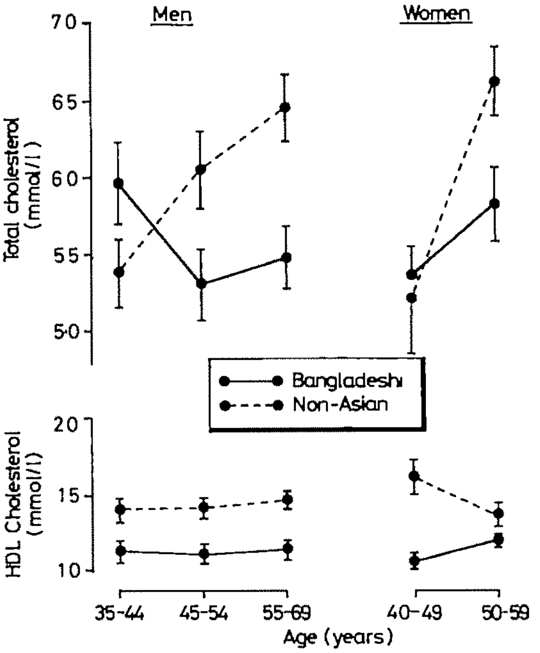

Fig 1 *Concentrations of plasma total cholesterol and high density lipoprotein cholesterol by age, sex, and ethnic category.*

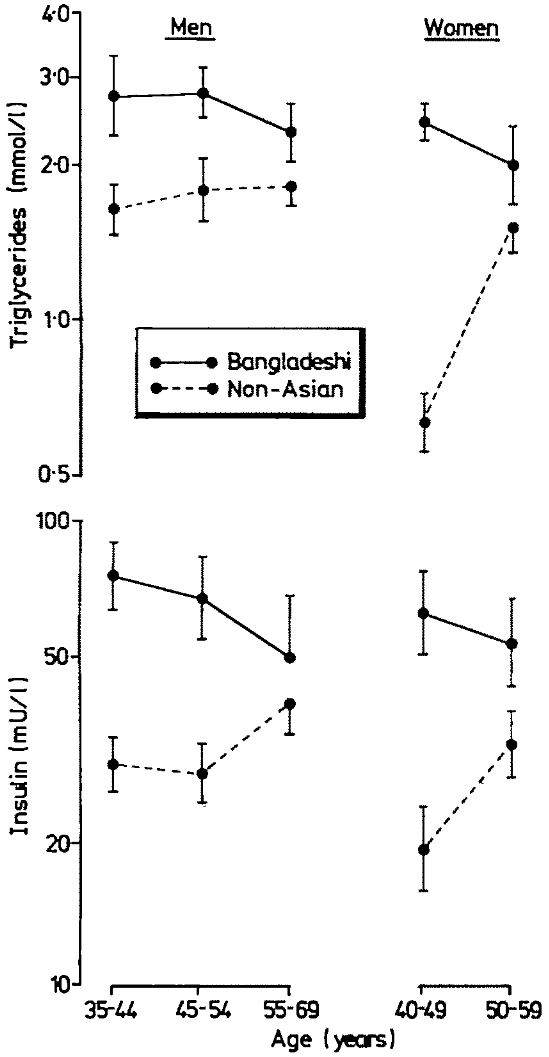

Fig 2 *Concentrations of plasma triglycerides and serum insulin by age, sex, and ethnic category.*

cigarette smokers, only 23% smoked > 15 cigarettes daily compared with 34% of non-Asian men. Ninety three per cent of Bangladeshi men and all Bangladeshi women were abstainers from alcohol.

CLINICAL AND LABORATORY FINDINGS (TABLES 2 AND 3)

Average systolic blood pressures were 10 mm Hg lower in Bangladeshis than in non-Asians and about half of this difference disappeared after adjustment for body mass index. Concentrations of high density lipoprotein cholesterol were much lower and those of triglycerides much higher in Bangladeshis. The relation between age and systolic blood pressure, plasma cholesterol, plasma triglycerides, and serum insulin was less pronounced in Bangladeshis than in non-Asians (figs 1 and 2). The proportions of essential fatty acids of the $\omega 6$ series (predominantly linoleic acid) in plasma lipids and the polyunsaturated/saturated ratio were lower in Bangladeshis than in non-Asians (table 3). Concentrations of fatty acids of the $\omega 3$ series were slightly higher in the Bangladeshis: this is consistent with their high consumption of fish. Values for factor VII coagulant activity correlated with plasma cholesterol, but only part of the difference in factor VII activity between Bangladeshi and non-Asian men was explained by the difference in plasma cholesterol.

More than 20% of Bangladeshi men and women had diabetes. This was three times the rate in non-Asians (table 4). Two thirds of those with diabetes were already diagnosed: this proportion was similar in both groups. Serum concentrations of insulin after a glucose load were about twice as high in Bangladeshis as in non-Asians (fig 2). This difference persisted after controlling for the time of sampling. The insulin/glucose ratio was also higher in Bangladeshis. Insulin concentrations correlated with body mass index within each group. Insulin and triglyceride concentrations correlated with each other and inversely correlated with high density lipoprotein cholesterol: some of the difference in the concentrations of high density lipoprotein cholesterol between Bangladeshis and non-Asians was accounted for by the differences in plasma insulin and triglycerides.

Discussion

Although the surname analysis of deaths of Asians nationally[2] and the 1970–72 register[6] suggest that the high rates for coronary heart disease in immigrants from the Indian subcontinent in Britain are shared by the Bangladeshi population of Tower Hamlets, it is difficult to confirm this by analysis of local mortality data because the numbers of deaths are small. During 1979–83 there were 49 deaths from coronary heart disease among men born in Bangladesh aged 20–69 who were resident in Tower Hamlets; the standardised mortality ratio for coronary heart disease in Bangladeshi men was 118 (95% confidence interval 85–151) and the proportional mortality ratio was 132 (95% confidence interval 105–176). These estimates are consistent with the national data for coronary heart disease mortality in immigrants from the Indian subcontinent (South Asians). Bangladeshi women in Tower Hamlets are not yet old enough for

Table 2 *Risk factors (mean (SE), age adjusted for all variables except height) for coronary heart disease by sex and ethnic category*

	Men		*Women*	
Risk factor	*Bangladeshi*	*Non-Asian*	*Bangladeshi*	*Non-Asian*
Current smokers (%)	82	45	22	39
	p < 0·001		NS	
Height (cm)	165 (1)	171 (1)	151 (1)	160 (1)
	p < 0·001		p < 0·001	
Body mass index (kg/m²)	23·9 (0·4)	26·6 (0·4)	23·7 (1·0)	26·1 (0·7)
	p < 0·001		p = 0·06	
Systolic blood pressure (mm Hg)	119 (2)	129 (2)	113 (3)	123 (3)
	p < 0·001		p < 0·05	
Diastolic blood pressure (mm Hg)	78 (1)	81 (1)	75 (3)	78 (2)
	NS		NS	
Plasma fibrinogen (g/l)	3·03 (0·11)	3·14 (0·10)	3·04 (0·12)	3·17 (0·09)
	NS		NS	
Plasma factor VIIc (% of reference value)	90 (4)	105 (3)	97 (7)	99 (1)
	p < 0·01		NS	
Plasma total cholesterol (mmol/l)	5·53 (0·15)	6·02 (0·13)	5·37 (0·25)	6·09 (0·18)
	p < 0·05		p < 0·05	
Plasma HDL cholesterol (mmol/l)	1·13 (0·04)	1·43 (0·04)	1·19 (0·08)	1·45 (0·05)
	p < 0·001		p < 0·05	
Percentage of total cholesterol as HDL	21·3 (1·0)	25·3 (0·9)	22·4 (1·5)	25·2 (1·0)
	p < 0·01		NS	
Plasma triglycerides (mmol/l)	2·59 (0·22)	1·76 (0·13)	1·77 (0·26)	1·10 (0·11)
	p < 0·001		p < 0·01	
Serum insulin (mU/l)	65 (8)	32 (4)	57 (13)	27 (4)
	p < 0·001		p < 0·01	

HDL, high density lipoprotein.

deaths from coronary heart disease to be common in this group (two deaths observed during 1979–83, 1·8 expected).

This study confirms that the excess of coronary heart disease among South Asians in Britain is not explained by raised concentrations of plasma cholesterol. Though no direct dietary measurements were made in this study, the low plasma cholesterol and low polyunsaturated/saturated ratio in plasma lipids are consistent with lower intakes of total fat in Bangladeshis than non-Asians, if the Keys equation[12] (a standard formula for predicting plasma cholesterol from dietary fat intake) holds. It is unlikely that the high dietary total fat intake and polyunsaturated/saturated ratio reported in a study of 12 Bangladeshi men in this district are representative of the average diet of this population.[13] The relatively high plasma cholesterol of Bangladeshi men aged under 45 years suggests that this group may be following a less traditional diet. The high proportion of smokers among Bangladeshi men differs from the low smoking rates of South Asian men recorded in north west London[4] and in a nationally representative sample.[14] The low concentrations of polyunsaturated fatty acids of the ω6 series in Bangladeshis contrast with the very high concentrations in Hindus in north west London. Although smoking and a low ratio of dietary polyunsaturated/saturated fat may contribute to the high rate for coronary heart disease of Bangladeshi men in East London, they cannot explain the national mortality pattern.

The high prevalence of diabetes, the hyperinsulin-

Table 3 *Fatty acid composition of cholesterol esters by sex and ethnic category (mean (SE))*

	Men		*Women*	
	Bangladeshi (27)	*Non-Asian (44)*	*Bangladeshi (37)*	*Non-Asian (38)*
Saturated (%)	14·2 (0·3)	12·8 (0·2)	14·2 (0·2)	12·3 (0·2)
	p < 0·001		p < 0·001	
Polyunsaturated:				
ω6 series (%)	56·6 (1·4)	58·3 (1·1)	55·3 (0·9)	60·1 (0·9)
	NS		p < 0·01	
ω3 series (%)	2·78 (0·22)	2·23 (0·17)	3·38 (0·16)	2·72 (0·16)
	p = 0·05		p < 0·01	
Ratio of polyunsaturated to saturated	4·28 (0·18)	4·81 (0·14)	4·21 (0·14)	5·21 (0·14)
	p < 0·05		p < 0·001	

Table 4 *Frequency of diabetes by age, sex, and ethnic category*

Age (yr)	*Men*		*Women*	
	Bangladeshi	*Non-Asian*	*Bangladeshi*	*Non-Asian*
35–44	2/17	1/22	1/2	0/12
45–54	10/32	4/34	9/36	0/11
55–64	4/22	3/28	0/3	3/18
All, age-adjusted	22%	10%	23%	4%

Odds ratio Bangladeshi : non-Asian = 3·1 (p < 0 01).

aemia after a glucose load, the high concentrations of plasma triglycerides, and low concentrations of high density lipoprotein cholesterol found in this South Asian population are all factors associated with increased risk of coronary heart disease in other populations: they appear to be part of a general pattern found in South Asians overseas and may represent different manifestations of a single metabolic disturbance. The 22% prevalence of diabetes in this small sample is similar to the figure reported for other populations of South Asians overseas[15-17] but much higher than the 1·3% in a comparable survey in East Pakistan in 1964.[18] Plasma concentrations of insulin have been reported to be higher in Asians than Europeans in South Africa[19,20] and in a hospital-based sample in West London.[21] High concentrations of triglycerides and low concentrations of high density lipoprotein cholesterol in South Asians compared with Europeans have also been reported in Trinidad[22] and the United States.[23,24] In our small sample there was no sex difference in the concentrations of high density lipoprotein cholesterol in either the Bangladeshi or the other groups: while absence of sex difference has been reported in other South Asian populations[4,25,26] the absence of the usual sex difference of about 0·3 mmol/l in the European group is puzzling since the 95% confidence interval for the difference (−0·15 to +0·15 mmol/l) is less than the usual difference and it is therefore unlikely to be explained entirely by chance or random measurement error.

Associations between raised concentrations of plasma insulin, high concentrations of triglycerides, and low concentrations of high density lipoprotein cholesterol have been reported in other populations[27-29]: hyperinsulinaemia increases the synthesis of very low density lipoprotein triglyceride synthesis[27,30] and this may have a reciprocal effect on the concentration of high density lipoprotein cholesterol.[31] Definitive demonstration of insulin resistance requires steady state measurements of glucose disposal and insulin concentrations, but the parallel findings of a raised insulin/glucose ratio and high frequency of diabetes in this South Asian population make it reasonable to infer that insulin resistance underlies the increased insulin concentrations.

The high insulin concentrations in Bangladeshis were not explained by high body mass index; however, this index may be inappropriate for comparing adiposity in groups with different mean frame sizes.[32] In other populations insulin concentrations are more closely related to deposition of fat on the upper body, which was not measured in this study, than to body mass index.[33] Pathological and epidemiological evidence support the view that the combination of raised plasma insulin, raised triglycerides, and low concentrations of high density lipoprotein cholesterol is atherogenic.[34-36]

Our results and those of other investigators indicate that the evidence relating to high fat diet, plasma cholesterol, hypertension, and smoking to the occurrence of coronary heart disease does not account for the high rates of coronary heart disease rates in South Asians overseas[5,15]; any attempt at an explanation must therefore invoke less well established risk factors. On the basis of these findings we suggest a unitary hypothesis for the mechanism of high rates of coronary heart disease and diabetes in South Asians overseas: insulin resistance may be responsible for hyperinsulinaemia, secondary disturbances of lipoprotein metabolism, and a high prevalence of non-insulin-dependent diabetes. This metabolic pattern might lead to accelerated atherogenesis either through a direct effect of insulin upon the arterial wall or as a result of the changes in lipoprotein concentrations. We are now planning a larger study to test this hypothesis and to investigate the relation of these metabolic differences to adiposity, diet, physical activity, and social environment. If the hypothesis is correct then measures to reduce hyperinsulinaemia, such as weight reduction and increased exercise, may be the most effective means of preventing coronary heart disease in South Asians.

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High prevalence of hypertriglyceridaemia and apolipoprotein abnormalities in coronary artery disease

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SUMMARY Serum lipids and apolipoproteins A-I and B were measured in 174 men aged < 60 with angiographically confirmed coronary artery disease and in 572 healthy control men. Two thirds of the patients had raised age-corrected values of fasting serum cholesterol and/or triglyceride and/or a low high density lipoprotein (HDL) cholesterol compared with the controls. Eighteen (30%) of the 61 normolipidaemic patients had a concentration of serum apolipoprotein A-I below the 5th percentile of 233 controls. In normolipidaemic patients on β blockers the relative prevalence of serum low density lipoprotein (LDL)-apolipoprotein B values above the 95th percentile of 339 controls was significantly increased. Discriminant function analysis showed that a raised concentration of serum triglyceride was the best discriminant between patients and controls, with raised LDL-apolipoprotein B and reduced apolipoprotein A-I coming second only to triglyceride in analyses where each was separately compared with all the lipid variables. These associations were highly significant and were independent of other influences, including β blockade.

These findings re-emphasise the importance of hypertriglyceridaemia as a risk factor and confirm that apolipoprotein abnormalities occur frequently in coronary disease, even in normolipidaemic patients.

Evidence that serum apolipoprotein measurements are useful indices of the risk of coronary heart disease was reviewed four years ago[1 2] and several reports have since appeared which further substantiate this concept.[3-9] Opinions are divided, however, as to whether increases in apolipoprotein B, the protein moiety of low density lipoprotein (LDL), or decreases in apolipoprotein A-I, the major protein of high density lipoprotein (HDL), correlate any better with angiographically defined coronary artery disease than do increases in LDL cholesterol or decreases in HDL cholesterol.[6-9]

The object of the present study was to assess the value of apolipoprotein measurements as risk factors by investigating the frequency of serum lipid abnormalities in medically treated patients with angiographically confirmed coronary artery disease and by determining how often apolipoprotein abnormalities occurred, especially in those patients found to be normolipidaemic.

Patients and methods

During the period June 1985–July 1986 all men below the age of 60 admitted to Hammersmith Hospital to undergo diagnostic coronary angiography or coronary artery bypass grafting had blood taken on the morning before these procedures, after an overnight fast, for measurement of serum lipids and apolipoproteins. Patients with diabetes, those on lipid lowering agents, and those who had already undergone coronary artery bypass grafting or had had a myocardial infarct within the preceding two months were excluded, as were those in whom the angiogram did not show significant coronary artery disease, defined as luminal stenosis of >50% in at least one vessel. Concentrations of serum total cholesterol and triglyceride were analysed enzymatically (Technicon Auto Analyzer methods SE4-0039 PE and SE-0065 FBI), as was serum HDL cholesterol after precipitation with heparin-manga-

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nese.[10] The concentration of LDL cholesterol was calculated by the formula of Friedewald *et al*[11] except in patients with triglyceride values of 4·5 mmol/l, in whom LDL cholesterol was measured after ultracentrifugation of serum.[12] Serum apolipoprotein A-I was measured by an immunoturbidometric method (Orion Diagnostica, marketed in the United Kingdom by Oxoid, Basingstoke, Hampshire) and LDL-apolipoprotein B by radial immunodiffusion, as originally described by Sniderman *et al*[13] and modified by Havekes *et al.*[14] Results were complete for 174 of the 188 consecutive patients who originally qualified for this survey.

Control values for fasting serum lipids and apolipoproteins were derived from symptom free men aged 20–60 with normal electrocardiograms who had undergone health screening at the British United Provident Association Medical Centre (BUPA), London between March 1983 and July 1986. Serum was obtained from 339 men for determination of LDL-apolipoprotein B and subsequently from another 233 men for determination of apolipoprotein A-I. Measurement of LDL-apolipoprotein B in patients with coronary artery disease and in controls was always performed by IT and apolipoprotein A-I was measured by DW. In all the controls, enzymatic analysis of total cholesterol, triglyceride, and HDL cholesterol (the last after dextran sulphate-magnesium precipitation)[15] was performed by JS Pathology Services on a Technicon SMAC System similar to that used at Hammersmith Hospital. To correct for interlaboratory differences multiple split sample assays were performed over a wide range of concentrations in each laboratory and conversion factors derived from these comparisons were used to make the Hammersmith Hospital values compatible with JS Pathology Services values.

There were no significant differences between the two control groups—their mean values of age, serum lipids, and lipoproteins being almost identical (table 1). These were therefore combined into one control group of 572 men for all case-control comparisons except those for apolipoprotein values. Because the patients with coronary artery disease were on average older than the controls (mean (SD) age of patients 50·4 (6·7) *v* mean age of controls 43·9 (8·5)) all lipid, lipoprotein, and apolipoprotein values were adjusted to the age of 45 by linear regressions techniques. Triglyceride values were log transformed before statistical analysis but untransformed values are given in the text and tables.

Statistical comparisons were undertaken with the aid of the NWA StatPak (Multifunction Statistics Library, Version 3.1, Northwest Analytical, Portland, Oregon) and SPSS/PC+ (SPSS, Chicago, Illinois). Discriminant function analysis was performed with BMDP statistical software (University of California Press, Berkeley, California).

Table 1 *Serum lipids in the two subgroups of controls (mean (SD))*

Variable	*Apo A-I controls* (*n* = *233*)	*Apo B controls* (*n* = *339*)
Age (yr)	44 (8)	44 (9)
Total cholesterol (mmol/l)	6·16 (1·10)	6·13 (1·05)
Triglyceride (mmol/l)	1·40 (0·74)	1·39 (0·70)
HDL cholesterol (mmol/l)	1·25 (0·30)	1·21 (0·29)
LDL cholesterol (mmol/l)	4·27 (1·05)	4·29 (1·00)

Apo A-I, apolipoprotein A-I; Apo B, apolipoprotein B.

Results

In the 174 patients with coronary artery disease the mean values of total cholesterol, triglyceride, and LDL cholesterol were higher, and those of HDL cholesterol were lower, than in the 572 controls ($p < 0·01$ for each pair of variables) (table 2). Apolipoprotein A-I values were lower and LDL-apolipoprotein B values were higher in patients with coronary artery disease than in their respective subgroups of controls ($p < 0·001$ in each instance). Figures 1–4 show the frequency distributions of concentrations of serum lipids and lipoproteins in patients with coronary artery disease and in controls; the distribution of triglycerides was positively skewed. High values of total cholesterol, triglyceride, and LDL cholesterol and low values of HDL cholesterol were more common in patients than in controls.

Figures 5 and 6 show the frequency distributions of the values for serum apolipoprotein A-I and LDL-apolipoprotein B in patients with coronary artery disease and the corresponding controls. Patients with coronary artery disease had a higher frequency of

Table 2 *Concentrations (mean (SD)) of serum lipid, lipoprotein, and apoprotein in patients with coronary artery disease and in controls*

Variable	*Patients* (*n* = *174*)	*Controls* (*n* = *572*)	*t*	*p*
Total cholesterol (mmol/l)	6·66 (1·34)	6·14 (1·07)	5·27	<0·001
Triglyceride (mmol/l)	2·43 (1·37)	1·40 (0·71)	—	—
Log$_{10}$ triglyceride (mmol/l)	0·34 (0·20)	0·10 (0·20)	13·56	<0·001
HDL cholesterol (mmol/l)	0·98 (0·29)	1·22 (0·29)	−9·70	<0·001
LDL cholesterol (mmol/l)	4·54 (1·05)	4·28 (1·01)	2·87	<0·004
Apo A-I (mg/dl)	126 (23)	145 (22)*	−8·49	<0·001
LDL-apo B (mg/dl)	137 (38)	113 (26)†	8·26	<0·001

*n = 233; †n = 339.

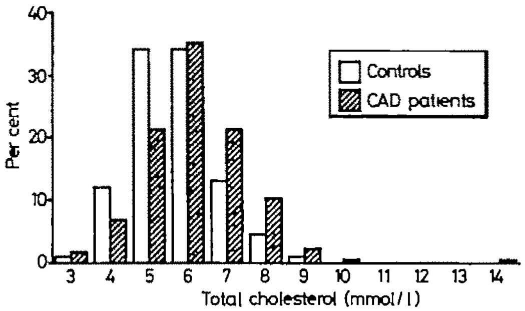

Fig 1 *Frequency distributions of serum total cholesterol in controls (n = 572) and patients with coronary artery disease (CAD) (n = 174).*

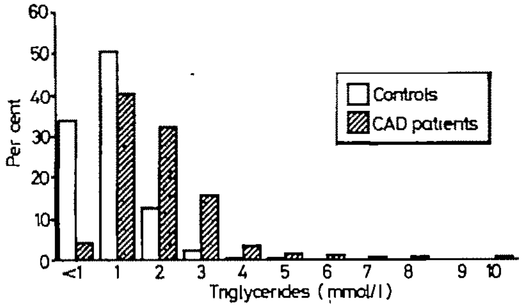

Fig 2 *Frequency distributions of serum triglyceride in controls and patients with coronary artery disease.*

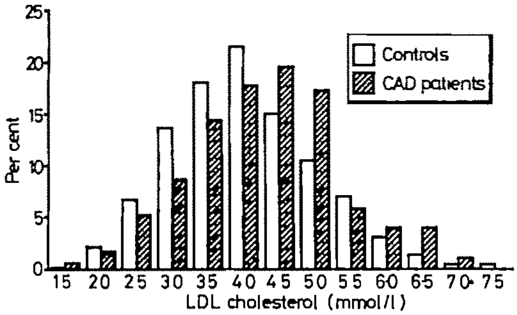

Fig 3 *Frequency distributions of LDL cholesterol in controls and patients with coronary artery disease.*

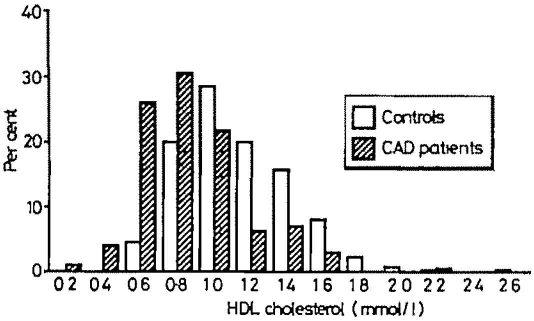

Fig 4 *Frequency distributions of HDL cholesterol in controls and patients with coronary artery disease.*

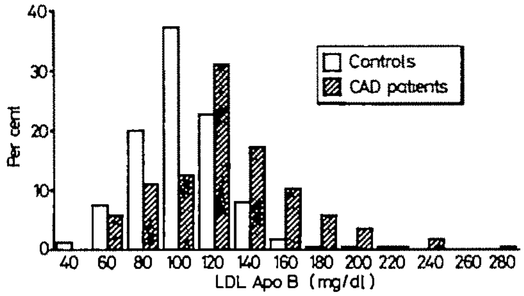

Fig 5 *Frequency distributions of LDL-apolipoprotein B in controls (n = 339) and patients with coronary artery disease.*

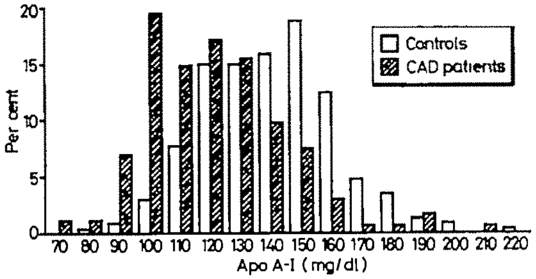

Fig 6 *Frequency distributions of apolipoprotein A-I in controls (n = 233) and patients with coronary artery disease.*

high LDL-apolipoprotein B values and low apolipoprotein A-I values than the controls, with less overlap between the two groups than was evident for LDL and HDL cholesterol (figs 3 and 4).

Table 3 shows the proportion of patients and controls with abnormal values of each measurement. For total cholesterol we used a cut off value of 6·7 mmol/l, which was the arbitrary upper limit of normal at the BUPA Medical Centre. For all the other variables, the 95th percentile or, for HDL cholesterol and apolipoprotein A-I, the 5th percentile values of the controls were used to define abnormality. The final column of this table gives the ratio or relative prevalence of an abnormal value in patients with coronary artery disease compared with controls and the 95% confidence intervals. Relative prevalence values were lowest with total cholesterol (1·59) and LDL cholesterol (1·64); LDL cholesterol

Table 3 *Proportions of abnormal values in patients and controls*

Value	*Patients (%)*	*Controls (%)*	*Relative prevalence (95% confidence interval)*
Total cholesterol > 6 7 mmol/l	42·0	26 4	1·59* (1 27–1 99)
Triglyceride > 2·78 mmol/l	29·9	4 9	6 11* (3·99–9·36)
HDL cholesterol < 0·80 mmol/l	31 0	4·9	6·34* (4·15–9 69)
LDL cholesterol > 6 05 mmol/l	8 0	4 9	1 64 (0·88–3·04)
Apolipoprotein A-I < 110 mg/dl	29·3	4·7	6 21* (3·34–11·56)
LDL apolipoprotein B > 153 mg/dl	26 4	4 7	5·60* (3·27–9 60)

*Relative prevalence differs significantly from unity ($p < 0{\cdot}001$).

did not differ significantly from unity. In contrast, abnormal values of triglyceride, HDL cholesterol, and each of the apolipoproteins were approximately six times more common in patients than in controls ($p < 0{\cdot}001$ in each instance).

FREQUENCY OF ABNORMAL APOLIPOPROTEIN VALUES IN NORMOLIPIDAEMIC PATIENTS

In those individuals with both normal total cholesterol and normal triglyceride (48% of the patients and 71% of controls) the relative prevalence of a low HDL cholesterol was 5·96 (95% confidence interval 3·35 − 10·61). None of these subjects had a raised LDL cholesterol value. Thirty five per cent of the patients with coronary artery disease and 68% of controls were normolipidaemic—that is they had normal concentrations of total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol. Table 4 shows the relative prevalence of apolipoprotein abnormalities in these normolipidaemic individuals. The relative prevalence of a low apolipoprotein A-I was significantly increased whereas that of a raised LDL-apolipoprotein B just failed to reach significance. The relative prevalence of a raised concentration of LDL-apolipoprotein B seemed to be higher in type IV individuals (raised triglyceride and normal LDL cholesterol) at 5·32 (0·78 − 36·35), but again this increase was not statistically significant.

CLINICAL CHARACTERISTICS OF PATIENTS WITH CORONARY ARTERY DISEASE

Serum lipid and apolipoprotein values in patients with coronary artery disease were similar irrespective of whether patients were admitted for angiography or coronary artery bypass grafting, presence or absence of previous myocardial infarction, and whether or not they were European. Table 5 shows the frequency of these and other characteristics. The lack of any racial difference in the concentraton of serum lipids is striking since only 7% of the controls were not European, whereas 20% of the patients with coronary artery disease were immigrants, generally from the Indian subcontinent. There was a family history of coronary heart disease in 57% of the patients with coronary artery disease, of whom three (2%) had tendon xanthomas, which are indicative of familial hypercholesterolaemia.

Table 4 *Proportions of abnormal apoprotein values in normolipidaemic patients and controls*

Variable	*Patients (%)*	*Controls (%)*	*Relative prevalence (95% confidence interval)*
Apolipoprotein A-I <110 mg/dl	29 5	5·6	5·31* (2·52–11·17)
LDL apolipoprotein B >153 mg/dl	6 6	1·8	3·69 (0·95–14 33)

*Relative prevalence differs significantly from unity ($p < 0\ 001$)

Table 5 *Clinical characteristics of patients*

Characteristic	*No*	*%*
Admitted for CABG	47	27
Previous MI	103	59
European	140	80
On β blockers	113	65
Family history of CHD	99	57
Cigarette smoking	74	43
Hypertension	33	19
Tendon xanthomas	3	2

CABG, coronary artery bypass grafting; CHD, coronary heart disease; MI, myocardial infarction.
Smokers currently smoked > 10 cigarettes/day or had given up less than a year before.
Hypertension was defined as a diastolic pressure > 100 mm Hg.

Treatment with β blockers was an important determinant of concentrations of HDL cholesterol and apolipoprotein A-I. Mean values (SD) were lower in the 65% of patients on these drugs (0·93 (0·27) mmol/l and 123 (23) mg/dl) than in those not taking them (1·06 (0·31) mmol/l and 130 (24) mg/dl), the difference in HDL cholesterol being significant at the 1% level. The effect of these drugs on triglycerides was less pronounced, with mean values in the two groups not differing significantly (2·56 (1·44) versus 2·20 (1·21) mmol/l), and this was also true of their effect on LDL-apolipoprotein B (139 (40) versus 132 (43) mg/dl). The relative prevalence of a raised LDL-apolipoprotein B was significantly increased in normolipidaemic patients, but only if they were on β blockers (5·27 with 95% confidence limits of 1·24 to 22·47, $p < 0{\cdot}05$).

Examination of the relation between smoking and concentrations of apolipoproteins A-I showed that mean values were lower (122 (20) mg/dl) in the 74 smokers than in the 100 non-smokers (128 (25) mg/dl), but this difference was not statistically significant. The mean value in the subgroup of 36 non-smokers not on β blockers was higher (132 (26) mg/dl) but it was still significantly lower than the mean value in controls (145 (22) mg/dl, $p < 0{\cdot}002$). This suggests that the low concentration of apolipoprotein A-I in patients with coronary artery disease was accentuated by, but not wholly attributable to, smoking and β blockade.

DISCRIMINANT FUNCTION ANALYSIS

Stepwise discriminant function analysis was performed, after log transformation in the case of triglycerides, as follows: (*a*) all lipid variables in all patients and controls; (*b*) all lipid variables and LDL-apolipoprotein B in all patients and the apolipoprotein B subgroup of controls; (*c*) all lipid variables and apolipoprotein A-I in all patients and the apolipoprotein A-I subgroup of controls.

In addition, each of the three analyses was performed separately on patients grouped according to whether they were (n = 113) or were not (n = 61) receiving β blockers. The results, shown in Table 6, indicate that triglyceride was the best discriminant between patients and controls, irrespective of β blockers, and that of the lipid variables HDL cholesterol was the next best discriminator. LDL-apolipoprotein B displaced HDL-cholesterol to third place whereas apolipoprotein A-I eliminated it altogether in analyses in which each apolipoprotein was evaluated separately against the lipid variables. However, the design of the study did not permit a comparison of LDL-apolipoprotein B versus apolipoprotein A-I. Total cholesterol was an independent variable only in patients not on β blockers.

Discussion

All case-control studies are by their nature opportunistic and therefore liable to unavoidable biases, unlike prospective surveys. Although this study is no exception it does give an impression of the pattern of risk factors present in men with newly diagnosed, symptomatic coronary disease in a routine clinical setting. Of the 174 patients with angiographically confirmed coronary artery disease just under 60% (104) had had a previous myocardial infarct. None had yet undergone any intervention other than treatment with antianginal drugs but 27% (47) were about to undergo coronary artery bypass grafting. Almost two thirds of the patients were on β blockers. The controls, who were drawn from men who had attended the BUPA Medical Centre for health screening during the previous three years, were free from symptoms or electrocardiographic evidence of coronary heart disease. Analysis of this group provided the cut off values used to define hyperlipidaemia and abnormally low concentrations of HDL cholesterol in patients with coronary artery disease and provided reference values for apolipoprotein A-I and LDL-apolipoprotein B. Despite possible differences in social class, occupation, and dietary habits the distribution of serum cholesterol concentrations in men attending the BUPA Medical Centre in London is known to be similar to that of men screened during the British Regional Heart Study,[16] who were chosen as being representative of the population at large.

Table 6 *Variables contributing independently to the discrimination between patients and controls ranked in order of importance ($p < 0{\cdot}001$ in every instance)*

Analysis	*All subjects*	*No β blockers*	*β blockers*
All lipids	(*a*) TG (*b*) HDL-C	(*a*) TG (*b*) HDL-C (*c*) TC	(*a*) TG (*b*) HDL-C
All lipids plus LDL-apo B	(*a*) TG (*b*) LDL-apo B (*c*) HDL-C	(*a*) TG (*b*) LDL-apo B	(*a*) TG (*b*) LDL-apo B (*c*) HDL-C
All lipids plus apo A-I	(*a*) TG (*b*) apo A-I	(*a*) TG (*b*) apo A-I	(*a*) TG (*b*) apo A-I

TG, triglyceride; TC, total cholesterol.
See text and footnote to table 1 for other abbreviations.

Serum concentrations of cholesterol and triglyceride in fasting patients and controls were measured in different laboratories by similar enzymatic methods. Two methods of precipitation were used to assay HDL cholesterol but the dextran sulphate-magnesium method used to analyse samples from controls gives results that are almost identical with the modified heparin-manganese method used in the patients.[17] Interlaboratory differences were minimised by applying appropriate correction factors. Apolipoprotein A-I and LDL-apolipoprotein B were always measured by the same operators, but on separate control groups. The validity of the radial immunodiffusion method used to assay LDL-apolipoprotein B was confirmed recently[18] and the immunoturbidometric method of measuring apolipoprotein A-I gives similar results to radial immunodiffusion[19] (E Bevan and I Trayner, unpublished).

Concentrations of serum cholesterol or triglyceride (or both) were increased in 52% of the patients with coronary artery disease and 29% of the controls. In the minority of Asian patients concentrations of serum lipids were similar to those in European patients. The finding that hyperlipidaemia was twice as common in patients with coronary artery disease accords with earlier studies,[20-22] and re-emphasises the importance of blood lipids in promoting atherosclerosis. The strength of the association between serum cholesterol and coronary heart disease mortality was underlined recently by the results of a very large prospective study,[23] which lend support to the earlier recommendations of the Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease.[24] This defined 6·7 mmol/l as the concentration of total cholesterol above which there is a high risk of coronary disease in those aged 40 and over. We and the BUPA Medical Centre used this value rather than the higher 95th percentile value to define hypercholesterolaemia.

The role of triglycerides is more controversial[25] but in the present study multivariate analysis showed that hypertriglyceridaemia was the most powerful discriminant between controls and patients. This finding accords with the results of the Stockholm prospective study[26] and with Castelli's recent reappraisal of data from the Framingham Study.[27]

Hypoalphalipoproteinaemia (HDL cholesterol <5th percentile) was also more common in the patients than in the controls (31% versus 5% respectively), and the odds ratio (six) was identical to that reported by Ordovas *et al.*[28] Several prospective studies have found HDL cholesterol to be correlated independently (and negatively) with coronary heart disease,[29 30] but the British Regional Heart Survey was an exception because HDL cholesterol was not predictive on multivariate analysis.[31 32]

The relative prevalence of abnormally high serum concentrations of apolipoprotein B in patients not taking β blockers who had normal LDL cholesterol concentrations was 5·38 (95% confidence interval 0·72–40·19) in those with raised serum triglycerides compared with 1·03 (95% confidence interval 0·24–4·38) for those with normal triglycerides. Despite the wide confidence interval for the former group, which reflects the small numbers studied, these findings provide additional evidence of a relation between hypertriglyceridaemia and abnormally high serum concentrations of apolipoprotein B.[33] Raised concentrations of apolipoprotein B have also been reported to correlate with a family history of premature myocardial infarction[34] and have been seen in the children of such individuals.[35] This suggests a genetic basis. The increased frequency of raised concentrations of apolipoprotein B in normolipidaemic patients on β blockers, which we saw, suggests that this syndrome can also be iatrogenic.

The main new finding in this study was the presence of abnormally low serum concentrations of apolipoprotein A-I (apolipoprotein A-I value < 5th percentile despite a normal serum concentration of HDL cholesterol) in almost one third of the normolipidaemic patients with coronary artery disease. Reduced plasma concentrations of apolipoprotein A-I have been noted in the first degree relatives of patients with coronary heart disease[36 37] including their children,[38] implying that this syndrome too has a genetic basis. In addition, environmental factors can influence plasma concentrations of apolipoprotein A-I; physical inactivity,[39] smoking,[40] and β blockers[41] all tend to reduce them. In the present study plasma concentrations of apolipoprotein A-I remained significantly lower in patients with coronary artery disease than in the controls, even when the influence of smoking and β blockers was taken into account.

Except for one small prospective study of apolipoprotein A-I[42] it remains to be established whether measurement of apolipoproteins can help to predict the risk of coronary heart disease. Analysis of restriction fragment length polymorphism of apolipoprotein genes may, however, help to define the usefulness of serum apoprotein assays as indices of genetically determined coronary disease, especially in normolipidaemic individuals.

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The role of risk factors in heart attacks occurring in men with pre-existing ischaemic heart disease

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SUMMARY The importance of three risk factors—serum total cholesterol, systolic blood pressure, and cigarette smoking—on the risk of new major ischaemic heart disease events in men who already have evidence of ischaemic heart disease was assessed. Data from the initial examination in a large prospective study of cardiovascular disease in middle aged men (the British Regional Heart Study) were used to separate 7710 men into three groups on the basis of a resting electrocardiogram, a standardised chest pain questionnaire, and recall of a doctor's diagnosis of angina or of a previous heart attack: (group 1) no evidence of ischaemic heart disease (75%), (group 2) evidence of ischaemic heart disease short of a definite myocardial infarction (20%), (group 3) definite myocardial infarction (6%). In the average follow up period of 7·5 years, 443 men suffered a new major event caused by ischaemic heart disease (fatal or non-fatal myocardial infarction or sudden cardiac death). Age standardised event rates were determined for each of the three groups for varying levels of the established risk factors. Cigarette smoking is strongly associated with the event rate in group 1 but in men with existing heart disease, especially group 3, differences in risk between the smoking categories were smaller. The strong relation between systolic blood pressure and event rate persisted in groups 1 and 2 but not in group 3. The positive association between serum concentration of total cholesterol and the event rate was strongest in group 1 and weaker in groups 2 and 3, though it remained highly significant.

These observations, taken together with the results of previous prospective studies and intervention trials, suggest that the important association between serum total cholesterol and the risk of heart attack persists in men with pre-existing ischaemic heart disease, including myocardial infarction. Therefore, in these men the reduction of serum total cholesterol concentration may be at least as important as it is in men without evidence of ischaemic heart disease.

Raised serum concentration of total cholesterol, high blood pressure, and cigarette smoking are well established risk factors for primary events in ischaemic heart disease. In men who have developed ischaemic heart disease, including survivors of acute myocardial infarction, the control of raised blood pressure and advice against smoking are well accepted in management. The importance of control of serum total cholesterol is more controversial and in general is not regarded as important.[1]

Follow up studies of myocardial infarction patients have shown that the most powerful predictors of ischaemic heart disease death within the first few months and years after a myocardial infarction are those which reflect the condition of the myocardium and the loss of ventricular function.[2] The findings of the few studies that have considered the predictive effect of serum concentration of total cholesterol (measured at least one month after the myocardial infarction) have resulted in uncertainty about its relevance in survivors of myocardial infarction.[3-7] A large prospective study of civil servants in London found that the serum concentration of total cholesterol was strongly associated with risk of death from ischaemic heart disease in those with evidence of pre-existing ischaemic heart disease.[8] Systolic blood pressure and cigarette smoking had weaker associations among men with evidence of ischaemic heart disease than in men initially free of the disease.

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Results from a large secondary prevention trial of cholesterol-reducing drugs suggest that they reduce the risk of ischaemic heart disease events.[9]

We present the results of the British Regional Heart Study, a large prospective study of ischaemic heart disease, which provide further evidence on the role of serum concentrations of total cholesterol and other major risk factors in men with evidence of ischaemic heart disease at the initial screening examination.

Patients and methods

The British Regional Heart Study examined 7735 men aged 40–59 years drawn at random from the age and sex registers of one general practice in each of 24 towns in England, Wales, and Scotland. The criteria for selecting the towns, general practices, and men have been described.[10 11] In brief, the 24 towns were taken from those with populations of 50 000–100 000 (1971 census). They covered the full range of mortality from cardiovascular disease and included all major geographic regions. The general practice in each town was required to have a social class distribution representative of that town. There was no attempt to exclude men with cardiovascular problems. The response rate was 78%.

Research nurses administered a questionnaire and examined each man. Details of the measurement of serum concentrations of lipids, blood pressure, smoking behaviour, electrocardiographic abnormalities, the man's recall of a doctor's diagnosis of heart disease, and the administration of a standardised chest pain questionnaire have all been reported.[10-15] Men were regarded as having angina if they had indicated on the questionnaire that they had chest pain on exertion (walking uphill or hurrying). This included definite and possible angina.[11]

CATEGORIES OF PRE-EXISTING ISCHAEMIC HEART DISEASE

The men were separated into three groups according to the extent of evidence of ischaemic heart disease present at screening.

Group 1.—Men with no evidence of ischaemic heart disease.

Group 2.—Men with evidence suggesting ischaemic heart disease short of a definite myocardial infarction. This group contains those with electrocardiographic evidence of definite myocardial ischaemia at rest but not definite myocardial infarction, those with angina or a possible myocardial infarction on chest pain questionnaire, or with a doctor's diagnosis of angina.

Group 3.—Men with a previous definite myocardial infarction according to electrocardiographic evidence or who recalled a doctor's diagnosis of a heart attack. About half the men with electrocardiographic evidence of a definite myocardial infarct had no history of chest pain.

FOLLOW UP

All men examined in 1978–80 are being followed up for cardiovascular morbidity and for mortality from all causes for eight years.[12] In the present analysis follow up (to December 1986) ranges from six and a half to eight years, with an average of 7·5 years, and follow up has been achieved for 99% of the original cohort. A new major event caused by ischaemic heart disease (fatal or non-fatal) occurred in 443 men—that is they became *cases*. A fatal event was considered to have occurred if ischaemic heart disease (ICD codes 410–414) was recorded as the underlying cause of death. Non-fatal myocardial infarction was diagnosed according to World Health Organisation criteria.[11]

STATISTICAL METHODS

Logistic regression models were fitted in order to standardise for age and other risk factors when we examined the association between a given risk factor and risk of an event caused by ischaemic heart disease.[16] The p values in figs 2 and 3 correspond to the risk factor fitted in its original continuous form. We tested for interaction between a given risk factor and ischaemic heart disease group by the likelihood ratio test.

Results

Table 1 shows the number of men and the number of cases in each of the three groups. Approximately 25% (1943) of the 7710 men for whom ischaemic heart disease group at screening is known had evidence suggesting the presence of ischaemic heart disease. The men in group 2 had about twice the risk of a future event as those in group 1. Those men who have evidence of a definite previous myocardial infarction (group 3) have more than six times the risk of men in group 1. The mean age increases with increasing strength of evidence of pre-existing

Table 1 *Occurrence of new major events caused by ischaemic heart disease in three groups according to evidence of ischaemic heart disease at initial examination (see Methods)*

	Group 1	*Group 2*	*Group 3*
New events	217	122	102
No of men	5767	1515	428
Event rate (per 1000/yr)	5·1	10·8	31·7
Mean age (yr)	49·8	51·1	53·3
Age standardised event rate (per 1000/yr)	5·3	10·5	28·4

Table 2 *Risk factor levels in three groups according to evidence of ischaemic heart disease at initial examination*

	Group 1	*Group 2*	*Group 3*
Cigarette smoking			
Never smoked (%)	25	21	13
Current smokers (%)	35	44	46
Systolic blood pressure:			
Mean (mm Hg)	144·0	148 7	148 2
% ≥161 mm Hg	18·3	25 0	24 3
Serum total cholesterol:			
Mean (mmol/l)	6 27	6 33	6 57
% ≥7·2 mmol/l	18 6	20·6	26·8

ischaemic heart disease. The age standardised rates show that age explains only a small proportion of the differences in crude event rates.

This report concentrates on three major risk factors for ischaemic heart disease: serum concentration of total cholesterol, cigarette smoking, and systolic blood pressure. Table 2 shows the levels of these risk factors for each of the three groups. The percentage of men who have never smoked decreased across the three groups while the percentage who are current smokers increased. For systolic blood pressure the mean value and the percentage in the top fifth of the overall distribution (≥161 mm Hg) were higher in those with existing ischaemic heart disease (groups 2 and 3). Mean systolic blood pressures were similar in groups 2 and 3. This could be because blood pressure tends to fall after a myocardial infarction or because of treatment with β blockers after myocardial infarction, or both. Mean serum concentrations of total cholesterol and percentages of men with concentrations ≥7·2 mmol/l (the top fifth of the overall distribution) increased progressively from group 1 to group 2 and from group 2 to group 3.

Figures 1–3 show the association between the risk factors at screening and the rate of major events caused by ischaemic heart disease in each of the three groups. For each risk factor the event rates are standardised for age alone, because standardisation for the other risk factors made very little difference to the results.

Figure 1 shows event rates for three categories of current cigarette smoking: never smoked cigarettes, ex-cigarette smoker, and current cigarette smoker. For men in group 1 there is a strong association between cigarette smoking state and risk of new events caused by ischaemic heart disease. The men who had never smoked cigarettes had the lowest rate, followed by the ex-cigarette smokers, and then by the current cigarette smokers. As one moves from group 1 through to group 3 the association between smoking state and the rate of events caused by ischaemic heart disease is somewhat reduced, in terms of the relative risk between smoking categories. In group 3 those who had never smoked were at lower risk than men in the other two smoking groups, although not significantly so, but there is little discernible difference in risk between the current smokers and ex-cigarette smokers. This may be because there was a smaller difference in the mean number of years men had smoked between the ex-smokers and current smokers in group 3 (9·5 years) than in the other two groups (13 years).

To examine the association with systolic blood pressure (fig 2) we divided the overall distribution into thirds. For men in groups 1 and 2 there is a strong and highly significant trend for the event rate to increase with systolic blood pressure. Among men with a previous definite myocardial infarction, however, there was no trend in event rates. One possible explanation for this might be that some men with systolic blood pressure in the lower two thirds of the distribution had had high values which were subsequently lowered by treatment, but that the risk level in these men did not fall correspondingly. This explanation seems unlikely, however, because the exclusion of all men who said they were taking antihypertensive drugs (22% of men in group 3) did not alter the trend.

To examine the association with serum concentrations of total cholesterol (fig 3) we again divided the distribution into thirds. In men with no sign of ischaemic heart disease at screening (group 1) there was a strong and highly significant tendency for the event rate to increase with the serum concentration of total cholesterol.

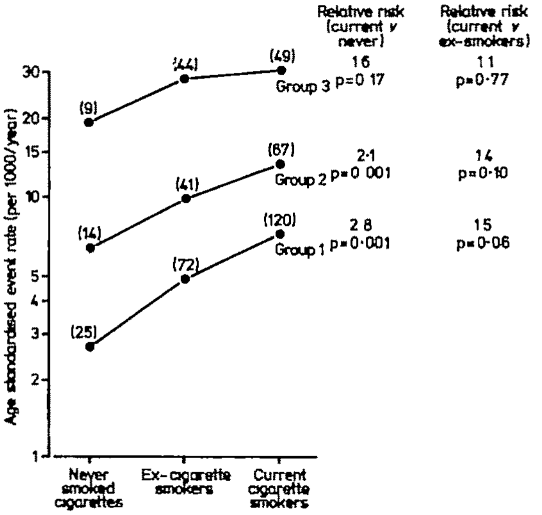

Fig 1 *Age standardised event rate by cigarette smoking state for each of three groups classified by evidence of ischaemic heart disease at initial examination. Numbers of cases are given in parentheses.*

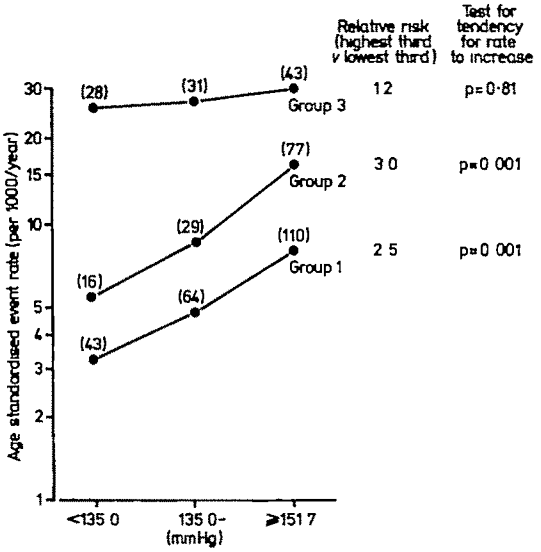

Fig 2 *Age standardised event rate according to distribution (thirds) of systolic blood pressure for each of three groups classified by evidence of ischaemic heart disease at initial examination. Numbers of cases are given in parentheses.*

This association was slightly reduced in men with existing ischaemic heart disease, but even in men with a previous definite myocardial infarction (group 3) a significant trend persisted ($p = 0{\cdot}01$).

Antihypertensive drugs (thiazides, propranolol) affect serum concentrations of lipids.[17 18] When men who said they were taking such drugs were excluded, the trend in group 3 was still apparent. As it was when men taking lipid lowering drugs (6% of men in group 3) were excluded.

The three major risk factors were acting simultaneously on the risk of new major events caused by ischaemic heart disease, and it is necessary to use multiple logistic models to determine the independent effect of each risk factor standardised for the effects of the other two risk factors. Table 3 shows the relative risk of a new major event caused by ischaemic heart disease for a specified difference in the level of the risk factor for each group. For each risk factor, the relative risk falls as one moves from group 1 to group 3, the decrease being least for serum total cholesterol, and more pronounced for systolic blood pressure and cigarette smoking. This decrease was statistically significant (in a test for interaction) only for systolic blood pressure ($p < 0{\cdot}05$). This statistical presentation confirms that standardisation for the other risk factors, in addition to age, makes little difference to the findings presented in figs 1–3. In table 3 only the relative risks in the three ischaemic heart disease groups can be compared for each risk factor; the relative risks within each ischaemic heart disease group—that is, vertical columns—cannot be compared.

Discussion

These results from the British Regional Heart Study indicate that in men with pre-existing ischaemic heart disease, even in those with a previous myocardial infarction, the serum concentration of total cholesterol remains of prognostic importance. This finding is consistent with that from the Whitehall study of male civil servants in which the association between serum total cholesterol and risk of death from ischaemic heart disease was determined in 2700 men (130 events) with evidence of myocardial ischaemia (according to the electrocardiograph and chest pain questionnaire) and in 14 863 men (134 events) with no such evidence.[8] The association between serum total cholesterol and death from coronary heart disease was found to be as strong in those with evidence of ischaemic heart disease as it was in those without. Separate results were not given for those who had experienced a previous definite myocardial infarction.

Other prospective studies that have measured the prognostic importance of serum total cholesterol in men with a previous myocardial infarction have been based on the follow up of patients with myocardial

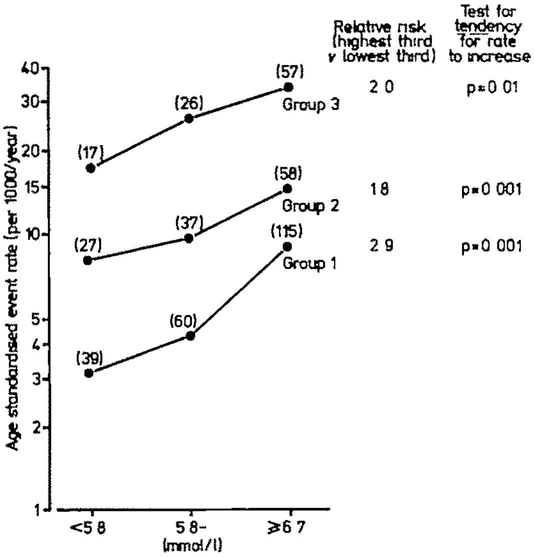

Fig 3 *Age standardised event rate according to distribution (thirds) of serum total cholesterol for each of three groups classified by evidence of ischaemic heart disease at initial examination. Numbers of cases are given in parentheses.*

Table 3 *Estimates of relative risk standardised for other risk factors in three groups according to evidence of ischaemic heart disease at initial examination*

		Relative risk		
Risk factor	*Comparison*	*Group 1*	*Group 2*	*Group 3*
Serum total cholesterol	1 mmol/l difference	1·5	1·5	1·3
Systolic blood pressure	10 mm Hg difference	1·2	1·2	1·0
Cigarette smoking	Current *v* ex	1·4	1·5	1·1
	Current *v* never	2·9	2·1	1·9

infarction, rather than being of a general population, as in the British Regional Heart Study. When studies with different sampling approaches concur this gives additional support to their findings. Table 4 summarises the studies.[3–7] The range of intervals from the index myocardial infarction to screening was wide. The few small studies in which cholesterol was measured within one month of the index myocardial infarction were not included because lipid concentrations are unstable in the first few weeks after myocardial infarction.[19] In the British Regional Heart Study the time since the previous myocardial infarction is unknown, but is likely to be several years.

By far the largest study in terms of the numbers of events, which is the factor of critical importance,[20] is the control group from the United States Coronary Drug Project.[6] The risk in those in the highest fifth of the distribution of serum total cholesterol was 50% higher than that in the lowest fifth ($p = 0{\cdot}001$). Results from the next three largest studies—Gothenburg,[5] the Aspirin Myocardial Infarction Study,[7] and the present study—generally accord with this finding. The relative risk in the British Regional Heart Study was higher, perhaps because some of the index myocardial infarctions (32%) were silent and presumably less severe. The two smallest studies, the New York Health Insurance Plan Study[3] and the Toronto study,[4] did not show that the relative risk increased with serum total cholesterol; however, the findings were not statistically significant. The results of these prospective studies accord with the findings from the Coronary Drug Project trial of the effect of cholesterol-lowering drugs on patients with myocardial infarction, by far the largest trial of cholesterol-lowering regimens among such subjects.[9] Results showed a significantly lower rate of events caused by ischaemic heart disease in those on cholesterol-lowering drugs than in controls. Other trials of cholesterol-lowering drugs or diets in survivors of myocardial infarction are much smaller but have tended to show a lower rate for events caused by ischaemic heart disease in the group on active treatment.[21] An overview of all randomised trials[22] of regimens for reducing cholesterol, primary or secondary, has shown that they significantly ($p < 0{\cdot}00001$) reduce the rate of events caused by ischaemic heart disease.

It seems that in men who have suffered a previous myocardial infarction serum concentrations of total cholesterol continue to be associated with risk of major events caused by ischaemic heart disease. In terms of relative risk, the strength of this association is smaller among these men than it is among those who have no signs of ischaemic heart disease (relative risks between high and low thirds of 2·9 and 2·0 for groups 1 and 3 respectively (fig 3). However, the *difference* (as opposed to the ratio) in risk rate between those with high and those with low serum concentrations of total cholesterol is greater in men with a previous myocardial infarction than in men with no signs of ischaemic heart disease. The difference in event rates between high and low thirds of the distribution of serum cholesterol is 18·4% (35·3–16·9%) for group 3 and 5·7% (8·8–3·1%) for group 1 (fig 3). Thus the attributable risk for total cholesterol is higher in men with a previous myocardial infarction because of the very high absolute values for risk. These findings suggest that the potential benefit of a policy of reducing cholesterol, in terms of the number of events postponed or prevented for a given number of men covered, is larger in men with a previous myocardial infarction than it is in men with no evidence of ischaemic heart

Table 4 *Summary of results from prospective studies on the prognostic importance of serum total cholesterol in men with a previous myocardial infarction (MI)*

Study	*Average time from index MI to screening*	*Number and type of new events*	*Estimated relative risk of new event*	*p value*
Coronary Drug Project (1978)[6]	3 years	748 (MI)	1·5	0·001
Gothenburg (1984)[5]	3 months	254 (death—any cause)	1·4	0·02
AMIS (1987)[7]	≃3 years	343 (CVD death)	1·3	<0·1
BRHS (1987)	—	100 (MI)	2·0†	0·01
HIP (1970)[3]	6 months	79 (MI)	0·6*	>0·1
Toronto (1970)[4]	3 years	55 (MI)	1·0*	>0·5

Relative risk compares extreme fifths, *halves, or †thirds.
AMIS, Aspirin Myocardial Infarction Study; BRHS, British Regional Heart Study; HIP, Health Insurance Plan Study; CVD, cardiovascular disease.

disease.

In the Whitehall study, the relative risk of mortality from ischaemic heart disease in men who were cigarette smokers at screening compared with those who were not was less in men with evidence of pre-existing ischaemia than in those without.[8] Similarly, in the control group of the Coronary Drug Project trial there was only a small (but statistically significant) difference in risk of coronary death or myocardial infarction between smokers and non-smokers.[23] These two sets of findings are consistent with our own. However, in neither the Whitehall nor the Coronary Drug Project reports were non-smokers divided into ex-smokers and those who had never smoked. This is unfortunate because results in the present report suggest that ex-smokers with a previous myocardial infarction experience a level of risk closer to that of current smokers than to that of those who have never smoked.

In the Whitehall Study, systolic blood pressure retained a moderately strong association with the risk of death from coronary heart disease in men with signs of ischaemia.[8] In the control group of the Coronary Drug Project trial, only a very small (non-significant) association between systolic blood pressure and risk of future coronary death or non-fatal myocardial infarction was found.[2] Once again, these results are consistent with our own. The reasons for the apparent lack of an association in men who have had a previous myocardial infarction are uncertain and do not appear to be explained by treatment. One explanation is that those men with the most severe impairment of left ventricular function by the myocardial infarction will tend to have lower blood pressure but higher risk of future events than other men.[24]

These findings from the British Regional Heart Study indicate that serum total cholesterol, a powerful risk factor for initial major events caused by ischaemic heart disease, influences the risk of such events in men with evidence of ischaemic heart disease, including those with definite previous myocardial infarction. This observation is supported by other prospective studies and by trials of regimens that reduce the serum concentration of total cholesterol in men with previous myocardial infarction. We conclude that reduction of serum concentrations of total cholesterol in men with any evidence of ischaemic heart disease is at least as important as it is in men without evidence of ischaemic heart disease.

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Differential sensitivity of radionuclide ventriculography for the detection of anterior and inferior infarction

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SUMMARY Attenuation of counts from the more distant inferior portion of the left ventricular blood pool in equilibrium radionuclide ventriculography may mean that inferior infarction is less likely to be detected than anterior infarction. Fourier amplitude and phase images can be used to map the extent and timing of regional ventricular wall motion and this study assesses their use for the detection of anterior and inferior infarction. Normal regional values of amplitude and phase were established in 38 individuals without evidence of cardiac abnormality. In 20 patients with anterior infarcts, though the sensitivity of the combined left anterior oblique amplitude and phase images was high (95%) it was lower (77%) in 39 with inferior infarcts, principally because the sensitivity of the phase image for the detection of inferior infarcts was only 39%. Right anterior oblique images generated from a first pass study detected all 13 patients with inferior infarcts. The mean left ventricular ejection fraction was significantly lower in the patients with anterior infarcts (37%) than in those with inferior infarcts (48%). Although the mean wall motion score on *x* ray contrast ventriculography was slightly lower in the patients with anterior infarction, the high sensitivity of the right anterior oblique amplitude and phase images in inferior infarction suggests that attenuation of counts is an important cause of reduced sensitivity of the left anterior oblique images. This may also partly explain the lower ejection fractions in inferior infarction.

It follows that both a right anterior oblique first pass study and a left anterior oblique equilibrium study are necessary for an accurate description of regional wall motion.

Radionuclide ventriculography permits the non-invasive evaluation of global and regional left ventricular function. Regional wall motion can be assessed by viewing a cine display of the ventriculogram, but the Fourier phase and amplitude images[1 2] provide a more objective assessment.[3] These images quantify the magnitude and timing of count changes in each pixel of the ventriculogram by assuming that the individual pixel activity-time curves approximate to the fundamental frequency of their Fourier transform. The amplitude image can be regarded as showing the extent of wall motion and the phase image as showing the time of minimum counts expressed as a fraction of the cycle. The parametric images show motion of all parts of the left ventricle and they differ from methods that display contours; these only show motion of walls that are perpendicular to the plane of projection. Together, the images detect abnormal wall motion because abnormalities of both the extent and timing of contraction occur after myocardial infarction.[4 5]

In the usual left anterior oblique projection, each left ventricular pixel represents a narrow column of blood passing from the anterior to the inferior wall. Changes in counts are the result of motion of both of the walls, and abnormal motion of either will lead to abnormalities of amplitude and phase. This may make it unclear which part of the ventricle is giving rise to an abnormality, but in practice the ambiguity can be resolved by the recognition of common patterns of wall motion. For instance, an amplitude defect in the centre of the left ventricle could represent either anterior or inferior hypokinesis, but

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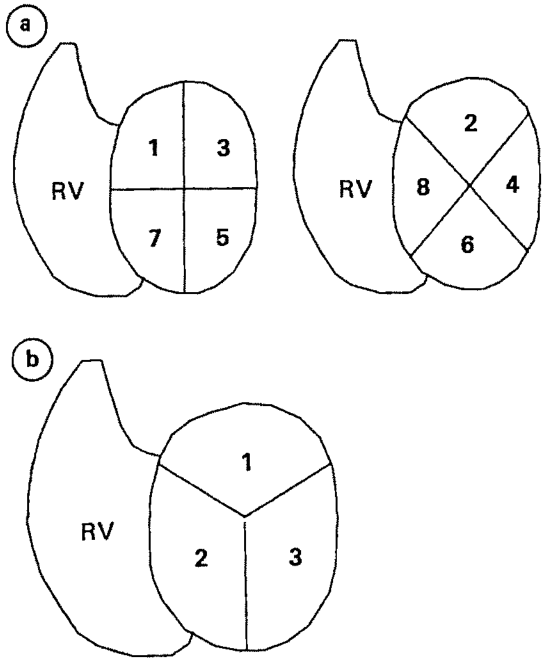

Fig 1 *The left ventricle was divided into eight overlapping quadrants in the phase image (a) and three sectors in the amplitude image (b). Mean values were calculated in each region.*

anterior hypokinesis is usually associated with septal hypokinesis whereas inferior hypokinesis is not.

A further problem arises from the attenuation of counts from the more distant portion of the blood pool, which means that abnormalities of amplitude and phase in inferior infarction may be small compared with those in anterior infarction. Often there is an amplitude defect in the centre of the left ventricular image, with a normal phase image, although there may be a small area of abnormally high phase at the apex if the inferior infarct is extensive. Small inferobasal infarcts may not be detected at all.

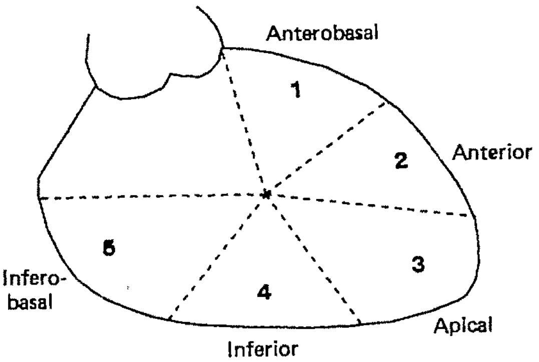

Fig 2 *The left ventricular perimeter on the x ray ventriculograms was divided into five segments and wall motion in each was assessed as hyperkinetic (3), normal (2), hypokinetic (1), akinetic (0), or dyskinetic (−1).*

We evaluated the differential sensitivity of amplitude and phase images obtained in the left anterior oblique projection in anterior and inferior infarction and the role of right anterior oblique first pass imaging.

Patients and methods

Equilibrium radionuclide ventriculography was performed in a left anterior oblique projection with a 30° caudal tilt after in vivo erythrocyte labelling with 740 MBq of technetium-99m sodium pertechnetate. We used a General Electric Portacamera IIC with a 200 mm field of view, interfaced to an Informatek Simmis III computer, to acquire 16 frames per cardiac cycle with electrocardiographic gating. There were 320 000 counts per frame and data from cycles that followed one lasting more than 115% of the mean were rejected. To compensate for the shortfall of counts in the final frame caused by short cycle lengths, each frame was standardised according to the number of cycles contributing to it. Fourier phase and amplitude images were generated after temporal and spatial smoothing. The left ventricular ejection fraction was calculated from count changes within a left ventricular region of interest after automatic background subtraction by means of a functional technique.[6]

First pass radionuclide ventriculography was performed in a right anterior oblique projection before the equilibrium study; the technique we used was described elsewhere.[7] Data were acquired in list mode and counts obtained during the passage of the bolus through the left heart were reformatted into a representative cine cycle of 16 frames. This usually included eight to twelve cardiac cycles, with 1000–4000 counts within the left ventricle at end diastole. Phase and amplitude images were generated in an identical fashion to the equilibrium study.

To establish normal regional values of amplitude and phase, we studied 38 subjects without evidence of cardiac disease. These were patients being investigated for suspected cardiac disease but in whom coronary arteriography and *x* ray contrast left ventriculography were normal. Values within two standard deviations of the mean in these subjects for the whole left ventricle and for eight quadrantic regions were regarded as normal (fig 1a). Amplitude was expressed as a percentage of the maximum amplitude within the left ventricle, and normal values were established for the whole ventricle and for three 120° sectors, representing the base, the anteroseptal wall,

Table 1 *Characteristics of the groups of patients with anterior and inferior infarcts*

Characteristic	*Anterior*	*Inferior*
Total number	20	39
Age (range)	52 (36–70)	54 (37–73)
Sex	19 M, 1 F	36 M, 3 F
ECG findings:		
Anterior or anteroseptal Q wave	16	0
Inferior or inferolateral Q wave	2	35
LBBB	0	2
Normal	2	2
Extent of disease:		
Three vessel disease	14	30
Two vessel disease	3	4
One vessel disease	3	5
Vessels diseased (occluded):		
LAD	20 (16)	34 (1)
LCx	17 (0)	30 (2)
RCA	14 (4)	39 (23)

ECG, electrocardiogram; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery; LBBB, left bundle branch block.

and the posterolateral wall (fig 1b).

Thirty nine patients with a single transmural inferior myocardial infarct and 20 with a single transmural anterior infarct were studied by radionuclide ventriculography (table 1). An equilibrium study in the left anterior oblique projection was performed in all patients, and a first pass study was performed in the right anterior oblique projection in 13 of the patients with inferior infarction. In each patient, mean regional amplitude and phase in the left anterior oblique images were compared with the results in patients without cardiac disease, and mean values in the right anterior oblique images were compared with previously established normal ranges.[7]

Infarction was diagnosed on the grounds of history, electrocardiographic changes, and abnormal wall motion on a right anterior oblique *x* ray contrast ventriculogram. The reasoning behind selection was to obtain two groups with abnormal motion that was as nearly as possible restricted to the anterior or the inferior left ventricle. Patients with Q waves in only the septal or the lateral leads were excluded, but those with Q waves in the septal or lateral leads in addition to the anterior or inferior leads were included. An experienced cardiologist who was not aware of the radionuclide findings analysed the *x* ray ventriculograms. The perimeter of the left ventricle was divided into five equal sectors representing the anterobasal, anterior, apical, inferior, and inferobasal areas (fig 2). In each area, wall motion was classified as hyperkinetic, normal, hypokinetic, akinetic, or dyskinetic. Patients with equal grades of abnormality of both the anterior and inferior walls were excluded, but patients with akinesia or dyskinesia of the anterior wall and hypokinesia of the inferior wall were included in the anterior group and vice versa. Patients with abnormalities in the apical sector were included in the anterior or inferior group according to whether adjoining abnormalities were present in the anterior or inferior wall.

Results

Table 2 shows the values for amplitude and phase in the normal individuals. There were no regional variations in phase, but mean basal amplitude was significantly lower than the global value ($p < 0\cdot01$) because of the overlap between the left atrium and ventricle. Amplitude in the septum was lower than in the lateral wall ($p < 0\cdot01$).

Table 3 shows the wall motion scores in the two groups of patients. The mean total wall motion score was slightly lower in those with anterior infarcts than in those with inferior infarcts, but the difference was not statistically significant ($p > 0\cdot05$ by Student's t test). The main regional abnormalities were in the anterior and apical regions (2 and 3) in anterior infarction, and in the inferior and inferobasal regions (4 and 5) in inferior infarction.

Mean (SD) left ventricular ejection fraction in the group with anterior infarcts was 37·2 (18·8)% and 48·0 (14·3)% in the group with inferior infarcts ($p < 0\cdot05$). Seventeen patients (85%) in the group with anterior infarcts and 23 patients (59%) in the group with inferior infarcts had abnormal ejection fractions (<50%).

Table 2 *Normal mean (SD) of amplitude and phase in the whole left ventricle (LV), and in the three regions shown in fig 1b for amplitude and the eight regions shown in fig 1a for phase*

	LV	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Amplitude:									
Mean (%)	58	51	55	62	–	–	–	–	–
SD (%)	5·0	6·9	4·2	5·1	–	–	–	–	–
Phase:									
Mean (°)	135	136	134	136	136	133	135	136	138
SD (°)	14	15	14	14	14	15	15	15	15

The amplitude values are expressed as percentage of the maximum value in the left ventricle.

Table 3 *Mean total and regional wall motion scores from x ray contrast ventriculography in the patients with anterior and inferior infarcts*

	Total	*1*	*2*	*3*	*4*	*5*
Anterior:						
Mean	4·9	1·9	0·3	0·1	0·9	1·7
SD	2·24	0·30	0·68	1·02	0·86	0·43
Inferior:						
Mean	5·4	1·9	1·5	1·2	0·5	0·3
SD	1·95	0·35	0·63	1·10	0·62	0·49

Regions 1 to 5 correspond to the anterobasal, anterior, apical, inferior, and inferobasal regions respectively (fig 2). The scores were assigned as: 3, hyperkinesis; 2, normal; 1, hypokinesis; 0, akinesis; −1, dyskinesis.

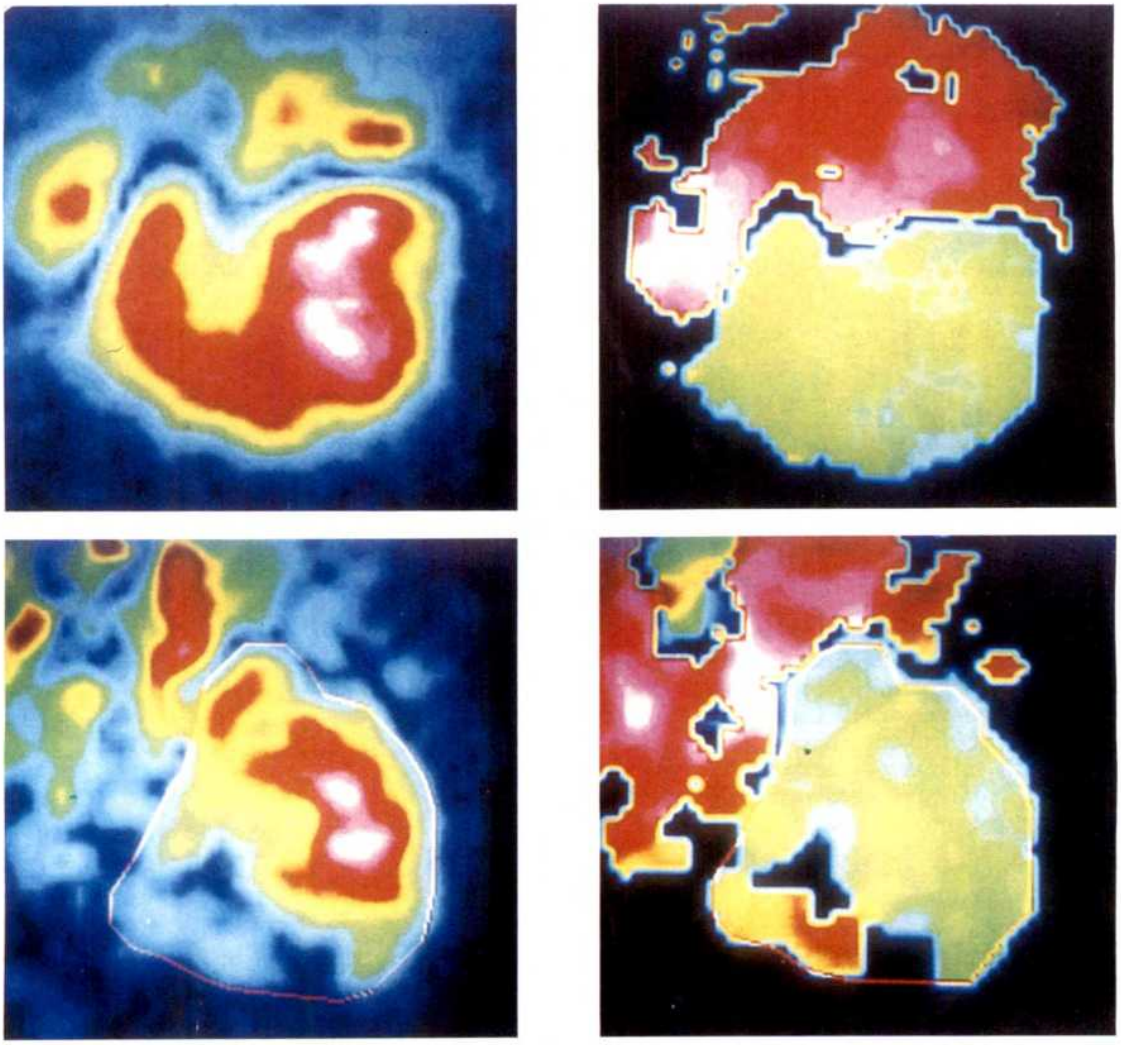

Fig 3 *Left anterior oblique (top) and right anterior oblique (bottom) amplitude (left) and phase images (right) in a patient with inferior infarction. The normal ventricular phase is green and there should be high values of amplitude within the left ventricle (red). The left anterior oblique images are normal apart from a slight reduction in lateral amplitude. The right anterior oblique images show inferobasal abnormalities.*

Table 4 *Numbers (%) of patients in the groups with anterior and inferior infarcts with abnormalities of the amplitude and phase images seen separately and in either the amplitude or the phase image obtained in the left anterior oblique projection*

	Amplitude	*Phase*	*Amp + phase*
Anterior	16 (80)	19 (95)	19 (95)
Inferior	26 (67)	19 (39)	30 (77)

Table 4 shows the numbers and percentages of patients with abnormalities in the amplitude and phase images obtained in the left anterior oblique projection. The images were more sensitive detectors of anterior infarction than of inferior infarction. The χ^2 test showed a significant difference in sensitivity for the phase image alone ($p < 0{\cdot}001$) but not for the amplitude image or for the two images combined ($p > 0{\cdot}05$).

The amplitude image obtained in the right anterior

Table 5 *Numbers (%) of patients with inferior infarcts (of the 13 studied in two projections) who had abnormalities of the amplitude and phase images in the left and right anterior oblique projections*

	Amplitude	*Phase*	*Amp + phase*
Left anterior oblique	7 (54)	4 (31)	7 (54)
Right anterior oblique	13 (100)	11 (85)	13 (100)

oblique projection was abnormal in all 13 patients studied in both projections and the phase image was abnormal in 11 (table 5). The χ^2 test showed a significant difference in sensitivity between right anterior oblique and left anterior oblique images for the detection of inferior infarction ($p < 0{\cdot}001$ for amplitude and $p < 0{\cdot}01$ for phase).

Figure 3 shows the findings in a patient with inferior infarction. The amplitude and phase images in the left anterior oblique projection are normal, but the right anterior oblique images both show abnormalities of amplitude and phase that are typical of infarction of the inferior wall.

Discussion

The results show that amplitude and phase images obtained in the left anterior oblique projection are highly sensitive (95%) detectors of anterior infarction but that they are less sensitive (77%) detectors of inferior infarction. Most of the loss of sensitivity was the result of the phase image, which was abnormal in 95% of patients with anterior infarction but in only 39% of those with inferior infarction. Because an abnormal value was defined as one that was more than two standard deviations from the normal mean, the specificity for each test was 97%.

There are two possible reasons for the reduced sensitivity. Attenuation of counts from the more distant inferior portion of the blood pool means that motion of the inferior wall of the left ventricle contributes less to changes in counts seen in each pixel. For a ventricle of average size the attenuation of counts from the inferior wall is approximately three times greater than that from the anterior wall. An alternative explanation is that the abnormalities of wall motion were less severe in the group with inferior infarcts. Global wall motion score in anterior infarction was less than in inferior infarction and though the difference was not statistically significant, there was a significant difference ($p < 0{\cdot}05$) between the two regions with the main abnormalities (anterior and apical for anterior infarction, and inferior and inferobasal for inferior infarction). Attenuation does not differ in the right anterior oblique projection, however, and because the right anterior oblique images were abnormal in every case of inferior infarction, attenuation must make a considerable contribution to the reduced sensitivity. If the severity of the abnormality of wall motion were the only explanation, then the amplitude and phase images would have been expected to be equally sensitive in the two projections.

It is difficult to explain why the sensitivity of the phase image is less than that of the amplitude image in inferior infarction. If two similar curves with different amplitude are summed, the resultant amplitude is equal to the mean amplitude of the components. Phase is a more complex variable, however, and it does not follow that summing two curves with different phase produces a curve with phase between that of the components. It is possible that a volume curve with high phase and low amplitude from the inferior portion of the ventricle, added to a normal curve from the anterior portion, results in a curve with reduced amplitude but normal phase.

Attenuation will also affect the calculation of ejection fraction and this has been shown in phantom studies by Schneider *et al.*[8] In patients with previous infarction, Reduto *et al* reported a mean left ventricular ejection fraction of 34% after anterior infarction and one of 50% after inferior infarction, measured by radionuclide ventriculography[9]; these values are similar to the 37% and 48% in this study. A lower ejection fraction after inferior infarction has also been described in *x* ray ventriculography,[10] but in view of the findings in this study, at least part of the difference must be because the radionuclide volume curve is weighted by counts from the anterior portion of the ventricle.

We found that amplitude and phase images obtained in the left anterior oblique projection were very sensitive detectors of anterior infarcts but less so of inferior infarcts. Much of the reduced sensitivity arose from the phase image. Right anterior oblique images were very sensitive detectors of both anterior and inferior infarcts. The findings can be accounted for by a combination of attenuation of counts from the inferior portion of the blood pool and less severe wall motion abnormalities in inferior infarction. The lower ejection fraction in anterior infarction is also partly the result of attentuation, and radionuclide ejection fraction is overestimated in inferior infarction. We believe that a combination of a right anterior oblique first pass study and a left anterior oblique equilibrium study gives the most reliable assessment of regional wall motion.

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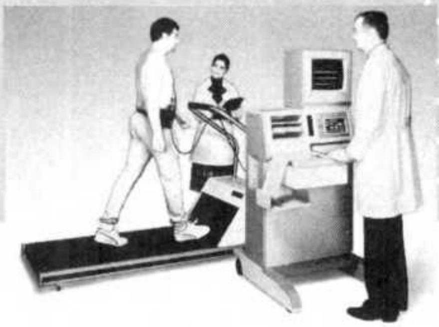

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Silent myocardial ischaemia in chronic stable angina: a study of its frequency and characteristics in 150 patients

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SUMMARY One hundred and fifty unselected patients with documented coronary artery disease were studied to establish the frequency and characteristics of silent myocardial ischaemia. Patients underwent ambulatory ST segment monitoring off all routine antianginal treatment (total 6264 hours) and exercise testing (n = 146). Ninety one patients (61%) had a total of 598 episodes of significant ST segment change, of which 446 (75%) were asymptomatic. Twenty seven patients (18%) had only painless episodes; 14 (9%) patients only painful episodes; 50 patients (33%) had both painless and painful episodes. The mean number of ST segment changes per day was 2·58 (1·95 silent); however, 11 patients (7%) had 50% of all silent episodes, and 48 patients (32%) had 91% of all silent episodes. Fifty nine patients (39%) had no ST segment changes on ambulatory monitoring, and 73 patients (49%) had no evidence of silent ischaemia. Episodes of silent ischaemia occurred with a similar circadian distribution to that of painful ischaemia, predominantly between 0730 and 1930. There was a similar mean rise in heart rate at the onset of both silent and painful episodes of ischaemia. Silent ischaemia was significantly more frequent in patients with three vessel disease than in those with single vessel disease, and was also significantly related to both time to 1 mm ST depression and maximal exercise duration on exercise testing. There was a highly significant relation between the mean number and duration of episodes of silent ischaemia in patients with positive exercise tests when compared with those with negative tests. No episode of ventricular tachycardia was recorded in association with silent ischaemic change.

It has been known for many years that myocardial infarction can occur in the absence of angina or its equivalents,[1 2] and since the introduction of ambulatory ST segment monitoring it has become clear that ST segment depression, the electrocardiographic hallmark of ischaemia, is a common finding in patients with coronary artery disease and is "silent" in most of them.[3-5] These silent ST segment changes have been shown to be truly ischaemic by various haemodynamic[6 7] and radionuclide[8-10] techniques.

The therapeutic and prognostic significance of silent myocardial ischaemia in patients with coronary artery disease and stable angina has yet to be elucidated. But if silent myocardial ischaemia is a frequent event in patients with coronary artery disease, angina or its equivalents may no longer be the primary features to be considered before proceeding to percutaneous transluminal coronary angioplasty or coronary artery bypass surgery, in view of the possible relation between silent ischaemia and both myocardial infarction[11-13] and sudden death.[11 14 15]

We studied 150 unselected patients with documented coronary artery disease off routine antianginal medications to establish the frequency and characteristics of silent myocardial ischaemia. Previous studies have reported smaller numbers, and some studies used highly selected patients.

Patients and methods

We studied 150 unselected patients with angiographically confirmed coronary artery disease. All patients had been referred for investigation of chest

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pain, or after myocardial infarction. There were 121 men and 29 women (mean age 55 years, range 33–77 years). All had clinically significant coronary artery disease. Sixty one patients had had at least one myocardial infarction. All patients underwent 24–48 hours of ambulatory ST segment monitoring off all routine antianginal medications, and 146 performed exercise testing according to the modified Bruce protocol. For each individual we recorded the details of anginal history, history of previous myocardial infarction, and previous angioplasty or coronary artery bypass surgery. We recorded the details of the resting electrocardiogram, left ventriculogram, coronary anatomy, and left ventricular ejection fraction.

EXERCISE TESTING

One hundred and forty six patients underwent maximal symptom limited treadmill exercise testing according to the modified Bruce protocol. Three patients were unable to exercise because of severe intermittent claudication and one could not cope with the treadmill. Electrocardiograms were recorded at the start of exercise and every three minutes thereafter and whenever chest pain, hypotension, or significant ST segment depression developed. A test was considered to be positive if there was ST segment depression of $\geqslant 1$ mm which was planar or downsloping and persisted for 0·08 s after the J point. Exercise was limited by the development of chest pain, dyspnoea, exhaustion, complex ventricular arrhythmias, or hypotension.

AMBULATORY ST SEGMENT MONITORING

All patients underwent 48 hours of ambulatory ST segment monitoring with pre-gelled electrodes to record two bipolar leads, an anterior lead CM5, and an inferior lead. The sites and method of application of these electrodes have been described elsewhere.[16] Two-channel recordings were then obtained on magnetic tape by a frequency modulated dual-channel recorder (Oxford Medilog 2, frequency response 0·05–40 Hz). The frequency response of this system is sufficient to record and display the ST segment accurately. The tapes were then visually analysed at 60 times normal speed by an Oxford Medilog MA20 scanner, and all printouts were at 25 mm/s. Significant ST segment depression was defined as planar or downsloping ST segment shift of $\geqslant 1$ mm measured 0·08 s after the J point that persisted for >30 s. Significant ST segment elevation was defined as an upward shift of the ST segment of $\geqslant 1$ mm at the J point compared with the resting recording. Changes in the T wave vector were not regarded as evidence of myocardial ischaemia unless they were accompanied by significant ST segment changes.

During the period of ambulatory monitoring, all patients kept a detailed angina diary to record the time of each episode of pain, the activity at the onset of symptoms, and the requirement for glyceryl trinitrate. They pressed an event marker on the ambulatory monitor at the onset of symptoms. This marked the magnetic tape, which meant that the electrocardiographic playback would automatically display the electrocardiogram at that time. All patients were encouraged to continue their normal activities during the period of monitoring.

COLLECTION OF DATA DURING AMBULATORY MONITORING

The following details were extracted and incorporated in the data bank: the heart rate immediately before and at the onset of each episode of ischaemia; the duration of each episode; maximal ST segment change; the relation of each episode to symptoms; the presence of arrhythmias, and whether they occurred in association with silent or painful episodes.

CARDIAC CATHETERISATION

In all patients we used either the Judkins or Sones technique for cardiac catheterisation. All angiograms were reported on independently by one of two senior radiologists, and a random selection were further reviewed by a cardiologist. Stenoses that reduced the luminal diameter of a major vessel by $\geqslant 70\%$ were regarded as significant. For the purposes of classification, significant left main coronary artery disease was regarded as two vessel disease.

The left ventricular ejection fraction was measured by a standard method, with two-frame analysis of the left ventriculogram in the right anterior oblique position.

STATISTICAL ANALYSIS

Bivariate statistics—We tested for the significance of relations between silent ischaemia and the variables of interest by non-parametric analysis. The Mann-Whitney U test, the Kruskal-Wallis test, or the Wilcoxon matched pairs signed ranks test was used, as appropriate.

Multivariate statistics—Discriminant function analysis was performed to ascertain which variables could be used to predict the frequency of silent ischaemia on ambulatory monitoring.

Results

FREQUENCY, DURATION, AND SEVERITY OF SILENT AND PAINFUL ISCHAEMIA

Five hundred and ninety eight episodes of significant ST segment change were recorded during 6264 hours of ambulatory ST segment monitoring. Four hundred and forty six episodes (75%) were asymptomatic. The mean duration of attacks (20·8 *v* 21·6 min) and mean severity of ST segment change (1·54 *v* 1·89 mm) were similar in both painless and painful episodes, as was the mean heart rate at the onset of both painless and painful episodes (95 *v* 99 beats/min). There was a significant increase in mean heart rate at the onset of both silent (86–95 beats/min, $p < 0·001$) and painful (88–99 beats/min, $p < 0·001$) ischaemia. There was no increase in heart rate at the onset of ischaemia in 163 instances (128 silent (29%), 35 painful (23%)). The mean number of ischaemic episodes per day was 2·58 of which 1·95 were silent. Fifteen (10%) patients had five or more episodes of silent ischaemia per day.

RELATION BETWEEN ISCHAEMIC CHANGES AND SYMPTOMS

Figure 1 shows the relation between ischaemic change on ambulatory monitoring and symptoms. Ninety one patients (61%) had one or more episodes of ischaemia. Fifty (33%) had mixed painful and painless episodes, and 27 (18%) had painless episodes only. Fifty nine patients (39%) had no ischaemic changes during 2548 hours of monitoring, and 73 patients (49%) had no silent ischaemic changes. Fifteen (10%) patients had 50% of all episodes of ischaemia, and 60 (40%) had 90% of total episodes. Eleven patients (7%) had 50% of episodes of silent ischaemia and 48 patients (32%) had 91% of the episodes of silent ischaemia (fig 2).

RELATION OF SILENT ISCHAEMIA TO CORONARY ANATOMY

Forty six patients (31%) had single vessel, 37 (25%) two vessel, and 67 (44%) three vessel coronary artery disease. Episodes of silent and total ischaemia were significantly more common in three vessel disease than in one vessel disease ($p < 0·05$) (fig 3). Mean ST segment depression in those with three vessel disease was also significantly greater during attacks than in those with single vessel disease ($p < 0·001$).

RELATION OF SILENT ISCHAEMIA TO EXERCISE TESTING

One hundred and forty six patients underwent treadmill exercise testing. One hundred and one (69%) patients had a positive test for ischaemia. Sixty four patients (63%) with a positive exercise test had at least one episode of silent ischaemia on monitoring. Eleven (25%) of the 45 patients with a negative exercise test had one or more episodes of silent ischaemia. Figure 4 shows the frequency distribution of silent ST segment change throughout the day. Only 15 (10%) patients had ≥5 episodes of silent ischaemia per day, and 14 (93%) of these had a positive exercise test at less than six minutes of exercise. One patient with a negative exercise test had documented coronary artery spasm.

We compared the mean heart rates at the onset of silent ischaemic change on monitoring with heart rate at 1 mm ST segment depression on exercise in 64 patients. The onset heart rate on ambulatory moni-

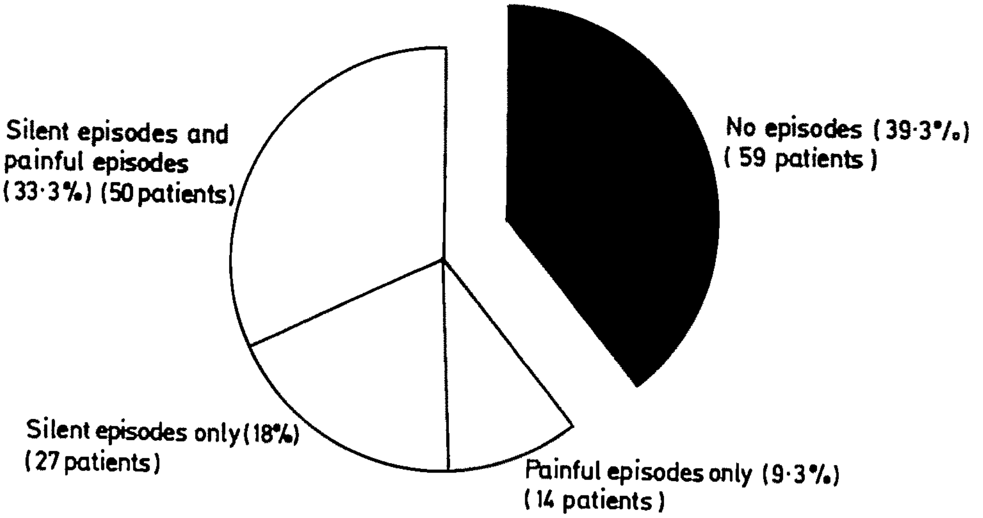

Fig 1 *Pie chart showing the percentage frequency of painless and painful ischaemia during 6264 hours of ST segment monitoring in 150 unselected patients with coronary artery disease.*

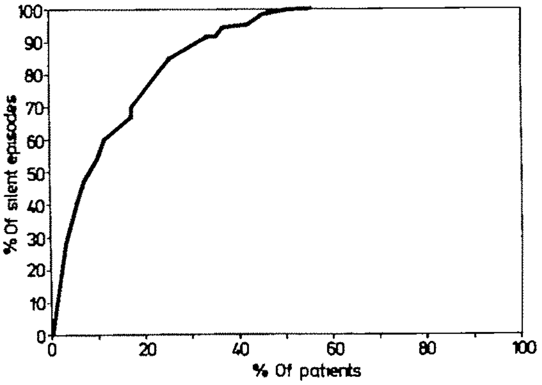

Fig 2 *Diagram showing the cumulative frequency of silent ischaemic episodes per day in 150 unselected patients with coronary artery disease. Over 50% of episodes occurred in 7% of patients and over 90% occurred in 32% of patients.*

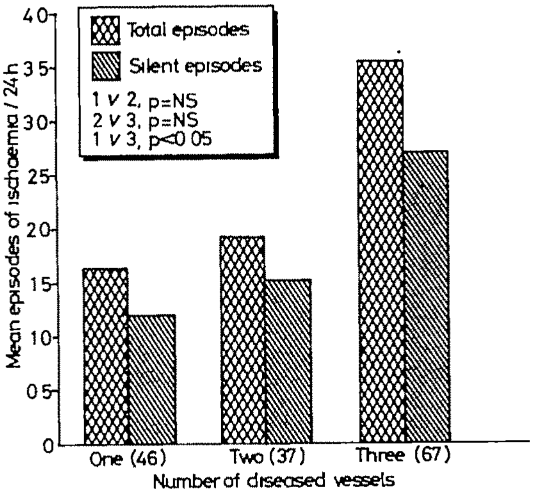

Fig 3 *Bar chart showing the mean frequency of total and silent ischaemic episodes per day in patients with coronary artery disease of different severity.*

toring was significantly lower than that on exercise testing (99 *v* 110 beats/min, $p < 0{\cdot}001$).

In the 101 patients with a positive test the mean number of episodes of silent ischaemia per day was 2·55 (range 0–33), compared with 0·67 (range 0–15) in those with a negative test ($p < 0{\cdot}001$). The mean duration of episodes of silent ischaemia per 24 hours was 54 minutes (range 0–554 min) in those with a positive test, compared with a mean of 9 min (range 0–109 min) in those with a negative test ($p < 0{\cdot}001$).

There was a significant relation between the mean number and duration of silent ischaemic episodes per day and (*a*) the exercise stage achieved before 1 mm ST segment depression developed ($p < 0{\cdot}01$, $p < 0{\cdot}01$ respectively) (fig 5) and (*b*) the time to maximal exercise ($p < 0{\cdot}001$, $p < 0{\cdot}01$ respectively).

We divided the positive exercise tests into those with <2 mm and those with ⩾2 mm ST segment depression, and we compared the mean number and duration of episodes of silent ischaemia on ambulatory monitoring in the two subgroups. No significant differences were noted. There was no association between the frequency of silent ischaemia and time taken for the electrocardiogram to become normal after exercise.

We compared the mean frequency and duration of episodes of silent ischaemia with the stage to maximal exercise in 45 patients with a negative exercise test. This confirmed a low frequency and duration of silent ischaemia in the subgroup as a whole, irrespective of stage to maximum exercise. Of the 43 episodes (9·6%) of silent ischaemia recorded in this group, 15 (35%) occurred in one patient with coronary spasm.

RELATION OF SILENT ISCHAEMIA TO LEFT VENTRICULAR EJECTION FRACTION AND A HISTORY OF MYOCARDIAL INFARCTION

The 89 patients who had not suffered a previous myocardial infarction tended to have an increased frequency of silent ischaemic episodes ($p = 0{\cdot}072$) that lasted significantly longer ($p < 0{\cdot}05$) than silent episodes in the 61 patients who had suffered one or more previous infarctions. The frequency of silent ischaemia was also inversely related to the presence of dyskinetic/akinetic areas on the left ventriculogram ($p < 0{\cdot}01$). There was no relation between left ventricular ejection fraction and silent ST segment change.

RELATION OF SILENT ISCHAEMIA AND THE FREQUENCY OF VENTRICULAR ARRHYTHMIAS

Thirteen patients (8·6%) had one or more recorded episodes of ventricular arrhythmia (ventricular bigeminy, multifocal ventricular extrasystoles, ventricular couplets, or ventricular tachycardia) during the 6264 hours of ambulatory monitoring. Six patients had episodes of unsustained ventricular tachycardia; however, none occurred in association with silent ischaemia.

CIRCADIAN DISTRIBUTION OF SILENT ISCHAEMIC EPISODES

Figure 6 shows the distribution of episodes of both total and silent ischaemia. Most episodes (67% of the total, 67% of the painless, and 68% of painful episodes) occurred in the twelve hour period between 0730 and 1930.

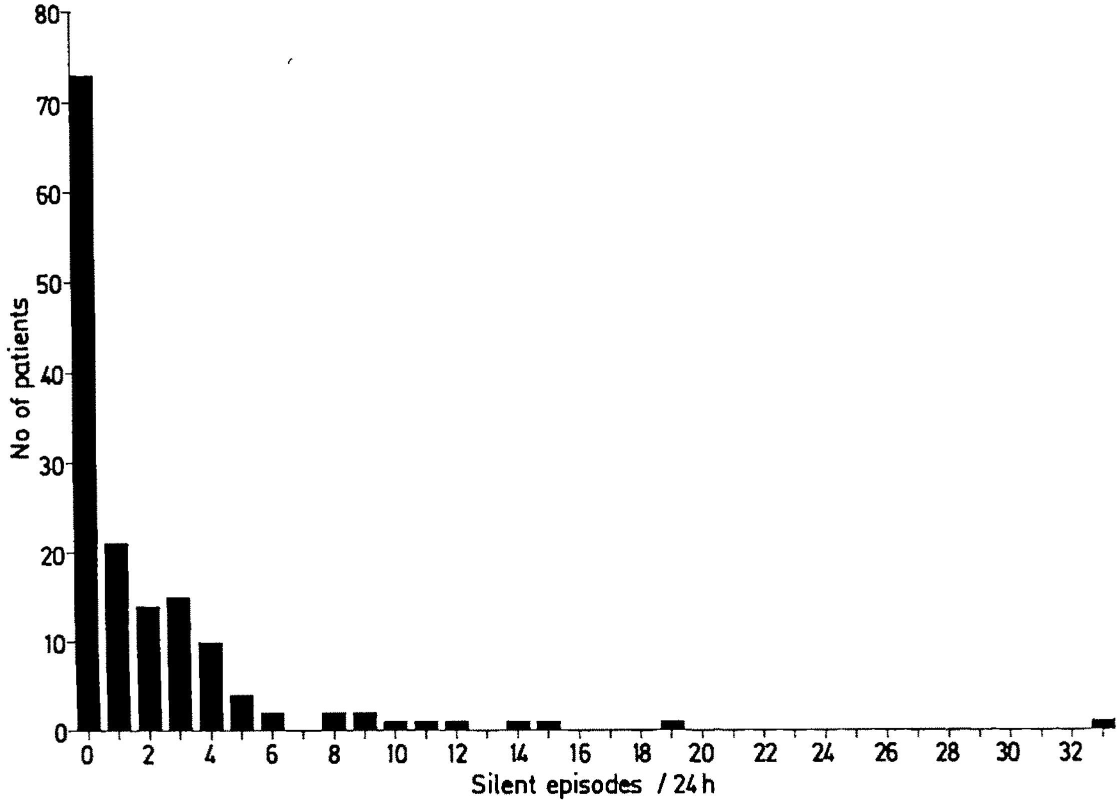

Fig 4 *Frequency distribution of silent ischaemic episodes per day in 150 unselected patients with coronary artery disease.*

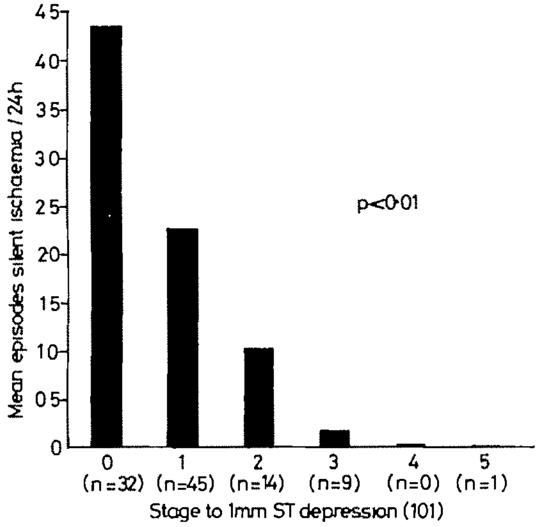

Fig 5 *Bar chart showing the relation between the mean episodes of silent ischaemia per day and stage to 1 mm ST segment depression on exercise testing.*

MULTIVARIATE ANALYSIS

To attempt to identify predictors of silent ischaemia we performed a stepwise discriminant function analysis with five variables (exercise test, maximal time of exercise test, previous myocardial infarction, number of vessels diseased, and left ventricular ejection fraction). As in the univariate analysis, the exercise test accounted for almost all the discriminating power in predicting the presence of silent ischaemia.

Discussion

This study describes the frequency, characteristics, and associations of silent myocardial ischaemia in patients with coronary artery disease. We have described a study population that differs from those of many previous investigators; our patients were unselected and the only criterion for inclusion in the study was clinically significant coronary artery disease. We can confirm earlier reports that silent ischaemia is common, and indeed 75% of all episodes of significant ST segment change were asymp-

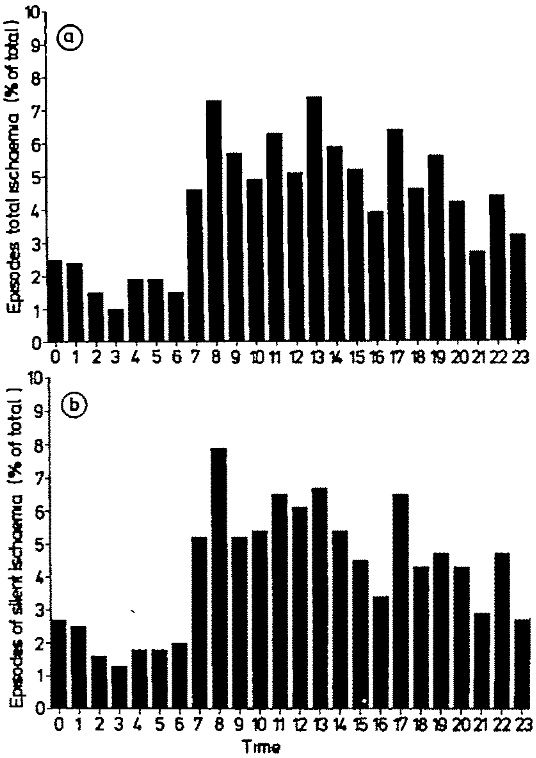

Fig 6 *Bar chart showing (a) the circadian distribution of total ischaemic episodes and (b) the circadian distribution of silent ischaemic episodes in 150 unselected patients with coronary artery disease.*

tomatic. Until now the frequency distribution of silent ischaemic episodes has not been examined in detail, and it has been suggested that most patients with angina may have frequent episodes of silent ischaemia.[17] We found that silent ischaemia was frequent in a small but appreciable proportion of the population of patients with coronary artery disease; however, almost half of the patients had no evidence of silent ischaemia on up to 48 hours of ambulatory monitoring, and over half of all silent ischaemic episodes occurred in only 7% of the patients.

We also examined the pathophysiological causes of silent myocardial ischaemia. The exact mechanisms by which silent ischaemia occurs are unknown, but many workers have reported that out of hospital episodes of ischaemia occur at a lower heart rate than the heart rate at the onset of 1 mm ST segment depression on exercise testing[8 18 19] and that this suggests that an increase in vasoconstrictor tone in the coronary vessels contributes to the genesis of ischaemia.[19] Rozanski *et al*, however, point out that although the heart rate at the onset of ischaemia is lower during mental stress than during exercise, there are substantial increases in systolic and diastolic blood pressure that increase the afterload to values seen during exercise and that catecholamine secretion, and possibly its rate of rise, might further contribute to significant increases in myocardial oxygen demand during stress, even if an increase in oxygen demand is not suggested by the change in heart rate.[20] We found that silent ischaemia does indeed occur at a lower heart rate than that at the onset of ischaemia on exercise testing, as also does ST change accompanied by angina. ST segment monitoring showed that the increases in heart rate to silent or painful ischaemia were not different. Also a similar proportion of silent and painful episodes of ST segment depression occurred in the waking hours. These findings indicate that the pathophysiological mechanisms of silent ischaemia do not differ from those of painful ischaemia. We found an increase in heart rate before the onset of ST segment depression in most episodes of ischaemia; but in approximately one quarter of instances heart rate did not increase before either the silent or the painful episodes.

Thus the same mechanisms seem to cause painful and painless myocardial ischaemia; and so drugs that are effective in the relief of angina should also be effective in the treatment of silent ischaemia, as has indeed been shown.[21]

The occurrence, frequency, and duration of silent ischaemia correlated most closely with the exercise test. The frequency and duration of silent ischaemia increased considerably in those patients with a positive exercise test at low workloads, thus confirming the findings of Quyyumi *et al*[16] and Cambell *et al.*[22] Indeed, in those patients whose exercise test was not positive until after stage 2 of the modified Bruce protocol, or whose exercise test was negative, silent ischaemia was very uncommon, which supports the assertion of Epstein *et al.*[23]

We also found a relation between the frequency of silent ischaemia and the extent of coronary artery disease, as did Kunkes *et al.*[24] This might be expected because the exercise test has been shown to correlate loosely with the extent of coronary disease. This relation, however, is much less close than that between silent ischaemia and the exercise test.

Interestingly, patients without a previous history of myocardial infarction had a non-significant trend towards more frequent episodes of silent ischaemia that lasted significantly longer than in patients with a history of myocardial infarction. This may be because patients who have suffered one or more previous myocardial infarctions have less viable myocardium capable of becoming ischaemic, and this is supported by the finding of significantly less silent ischaemia in patients with dyskinetic/akinetic segments on left ventriculography. Another explanation is that the electrocardiographic effects of previous myocardial infarction obscure alterations in the ST segment.

Finally, this study confirms that ventricular arrhythmias are relatively uncommon in unselected patients with coronary artery disease.[25] While a causative relation between silent ischaemia and ventricular irritability might be expected, this was not found in our subjects.

The results of this study do not imply that silent ischaemia is unimportant in clinical practice; however, it seems that silent ischaemia is probably most important in a small proportion of the population of patients with coronary artery disease. Where facilities for ambulatory monitoring are limited or not available, exercise testing should provide a means of identifying the majority of such patients, particularly if the test is positive at low workloads. Further studies will be necessary to determine the prognostic implications of silent ischaemia in patients with chronic stable angina, and whether the prognosis can be altered by medical or surgical treatment.

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Sequence of epicardial repolarisation and configuration of the T wave

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SUMMARY Epicardial activation and repolarisation sequences were investigated in patients with upright or inverted T waves in left ventricular leads of the surface electrocardiogram. Fifteen patients were studied: 10 were undergoing coronary artery bypass grafting (upright T waves) and five aortic valve replacement (four patients with T inversion). Monophasic action potentials were recorded intraoperatively from eight to 10 left ventricular sites in each patient. In patients with upright T waves there was an inverse relation between the duration of the monophasic action potential and the activation time (mean slope −1·44). As a consequence, activation and repolarisation proceeded in opposite directions. Dispersion of repolarisation time (14 ms) was less than dispersion of activation time (23 ms). In patients with T wave inversion caused by aortic stenosis there was no relation between the duration of action potential and activation time; the repolarisation sequence resembled the activation sequence, and the dispersion of repolarisation time was greater than the dispersion of activation time (31 and 26 ms respectively).

These results show that there are epicardial repolarisation gradients in man and that these are related to the configuration of the T wave. In patients with upright T waves an inverse relation between the duration of the action potential and the activation time reduces the dispersion of the repolarisation time. When the T wave was inverted this relation was no longer found and the dispersion of repolarisation increased.

The human ventricular activation sequence has been extensively studied. Knowledge of the normal activation sequence[1,2] has contributed to our understanding of the role of abnormalities of activation in arrhythmogenesis.[3] In contrast, little is known of the repolarisation sequence in health or disease. As a consequence the role of repolarisation abnormalities in arrhythmogenesis remains uncertain. Animal studies have shown that increased dispersion of repolarisation is arrhythmogenic,[4-6] but it has been difficult to assess dispersion of repolarisation in man. The contribution of regional differences in repolarisation to the genesis of the T wave of the surface electrocardiogram is similarly unclear.[7]

Repolarisation times can be accurately determined from monophasic action potentials.[8,9] The recent development of intraoperative techniques for recording monophasic potentials from the epicardium[10-12] offers the opportunity to undertake detailed repolarisation mapping in man. This study reports the sequence of epicardial repolarisation over the left ventricle of patients with upright T waves and patients with inverted T waves in the left ventricular leads of the surface electrocardiogram.

Patients and methods

PATIENTS

We studied 15 patients: 10 undergoing routine coronary artery bypass grafting and five undergoing aortic valve replacement. Patients undergoing bypass grafting had upright T waves in left ventricular leads of their surface electrocardiogram (leads I, aVL, and V3–V6) before operation. Patients undergoing

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replacement of the aortic valve had dominant aortic stenosis (catheter or Doppler gradients ranging from 60 to 110 mm Hg) and evidence of left ventricular hypertrophy but no or minimal aortic regurgitation. There was T wave inversion in the left ventricular leads of the preoperative electrocardiogram in four of the five patients with aortic stenosis. In all four patients, leads I, aVL, V5, and V6 showed an inverted T wave. T wave configuration in leads V3 and V4 was either biphasic or inverted (V3 three patients biphasic, one inverted; V4 two patients biphasic, two inverted). In the fifth patient T waves were upright in the left ventricular leads. Four of the five patients with aortic stenosis underwent coronary angiography and none had clinically significant coronary disease.

All patients were in sinus rhythm and none had bundle branch block. No patient had a history of arrhythmias or myocardial infarction and none was being treated with digoxin. Eight of the 10 patients undergoing coronary artery bypass grafting were taking β blockers.

All patients gave informed consent for mapping. The study was approved by the ethics committee of the hospital.

EPICARDIAL MONOPHASIC ACTION POTENTIAL RECORDING

We recorded monophasic action potentials intraoperatively from the epicardium using a hand held probe.[12] The probe was an electrode assembly mounted on a flexible spatula. The electrode assembly was made from two silver-silver chloride electrodes—a central blunted spike electrode, which protruded by 1 mm, surrounded by a flush mounted ring electrode (diameter 7 mm). Potentials were recorded through a purpose built amplifier (bandpass 0·007 to 100 Hz). The signals were displayed on a monitor, which was visible to the surgeon, and recorded on paper (Mingograf) and on magnetic tape (Racal Store 7). For ethical reasons, recordings were confined to the epicardium and the transmural signals were not investigated.

ELECTROCARDIOGRAPHIC MONITORING

Lead I of the surface electrocardiogram was monitored continuously. In three patients the amplitude of the T wave decreased after thoracotomy, but the T wave polarity remained constant. Because mapping required cardiac manipulation and changing the orientation of the heart, the surface electrocardiogram varied during mapping. At intervals during mapping and on its completion the surface electrocardiogram was recorded with the heart in its normal position: T wave configuration was unchanged.

EPICARDIAL MAPPING

The heart rate was maintained constant by right atrial pacing at a fixed rate 10–20 beats/min above the spontaneous rate. Mapping was undertaken on cardiopulmonary bypass to facilitate epicardial access and to minimise the haemodynamic consequences of cardiac manipulation. The patients' temperature was maintained within the range 36–37°C, as indicated by an oesophageal thermistor probe. Mapping was started after six minutes of bypass to avoid the transient changes in the duration of the action potential that occur in the first few minutes of bypass.[12]

Potentials were recorded from 10 sites over the left ventricle (fig 1). These sites covered most of the epicardium of the left ventricle. We did not attempt to map the most apical portion of the ventricle, because mapping this area did not give satisfactory results.[12]

We recorded from the 10 sites on four occasions, starting at a different site on each occasion to ensure that any time dependent changes would influence each site to the same extent. Mapping took approximately eight minutes.

DEFINITIONS AND MEASUREMENTS

Monophasic action potentials were acceptable if they showed an amplitude at least 4 mV, a smooth repolarisation phase, freedom from baseline artefact, and constancy of configuration over at least two consecutive cycles. Potentials were timed with respect to a fixed left ventricular reference electrode (bandpass 30 to 300 Hz) (fig 2).

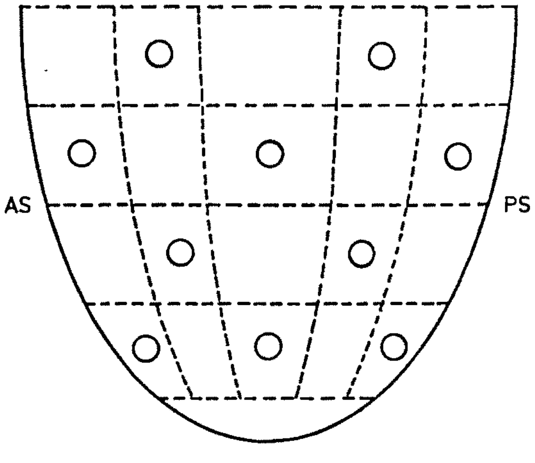

Fig 1 *Epicardial mapping sites. The left ventricle was considered as a grid. The ten sites indicated were mapped. AS, anterior septum; PS, posterior septum.*

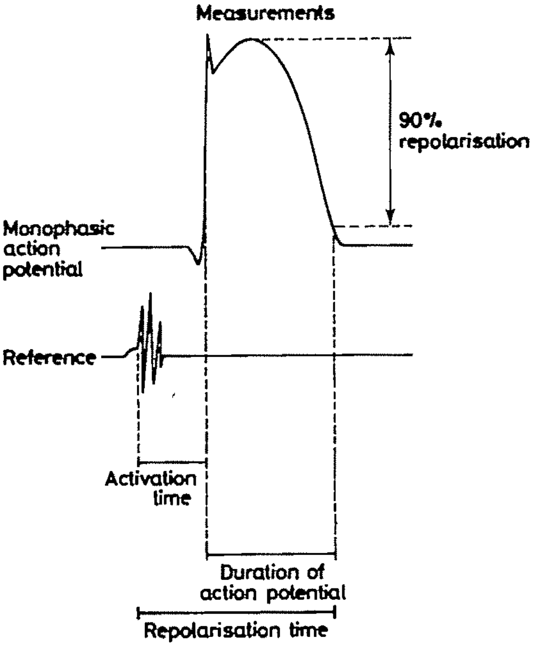

Fig 2 *Monophasic action potentials were timed in relation to a fixed ventricular reference electrode. Repolarisation time at any site is determined by the sum of activation time and action potential duration.*

The activation time was defined as the interval between reference and the visually determined time of maximum velocity of the upstroke of the monophasic action potential.

The action potential duration was defined as the interval between the time of maximum upstroke velocity and the time of 90% repolarisation from maximum plateau amplitude to baseline.

The repolarisation time was defined as the interval between reference and the time of 90% repolarisation—that is, the sum of the activation time and the action potential duration.

For each epicardial site we measured the activation time, action potential duration, and repolarisation time as the mean of the four individual probe applications at that site.

The dispersion of each variable was defined as the difference between the maximum and minimum values of the site means within each patient.

MEASUREMENT OF EPICARDIAL TEMPERATURE

We studied the variation in epicardial temperature in four of the patients undergoing bypass grafting by applying a small thermocouple probe directly to the epicardium. Temperature was recorded at each of the 10 sites used for mapping. The effects of cooling on the duration of the action potential were studied in three of the four patients. Monophasic potentials and temperature were recorded simultaneously during cooling and before cardioplegia. The probe was applied repeatedly at the same site and the heart rate was kept constant by atrial pacing.

STATISTICAL ANALYSIS

The duration of the action potential and the activation time at different epicardial sites were plotted and the regression line was calculated for each patient. Ninety five per cent confidence limits and the statistical significance of the slope of the regression lines were calculated.

Before comparison, values in different patients were normalised to eliminate differences caused by reference placement, the duration of action potential, and heart rate. For each patient, the results of all left ventricular sites were pooled to provide a mean activation time, action potential duration, and repolarisation time. The deviation of each site from the mean was then determined, thereby providing a normalised estimate of the relative timings of different sites. The normalised values for sites were pooled to determine a mean activation and repolarisation sequence for the study group.

Results

ACTIVATION AND REPOLARISATION SEQUENCES FOR UPRIGHT T WAVES

The activation time, action potential duration, and repolarisation time were studied in 10 patients with upright T waves. An inverse relation was seen between the duration of the action potential and the activation time (fig 3). The slope of the regression line for the duration of the action potential against the activation time was negative in all 10 patients (table 1). The 95% confidence limits for the slope varied in different individuals, achieving statistical significance in seven patients and borderline significance in two others.

Because the repolarisation time is determined by the sum of the activation time and the action potential duration, this inverse relation resulted in a relative uniformity of repolarisation times—in eight of the 10 patients dispersion of repolarisation time was less than dispersion of action potential duration (table 2). As a further consequence, the repolarisation time in individual patients was in general found to be independent of the activation time (fig 4a). The exception, patient 10, showed a significant inverse relation between repolarisation time and activation time (slope $-1{\cdot}09$, $p < 0{\cdot}025$), reflecting a particularly steep inverse relation between the activation time and the action potential duration (slope $-2{\cdot}09$).

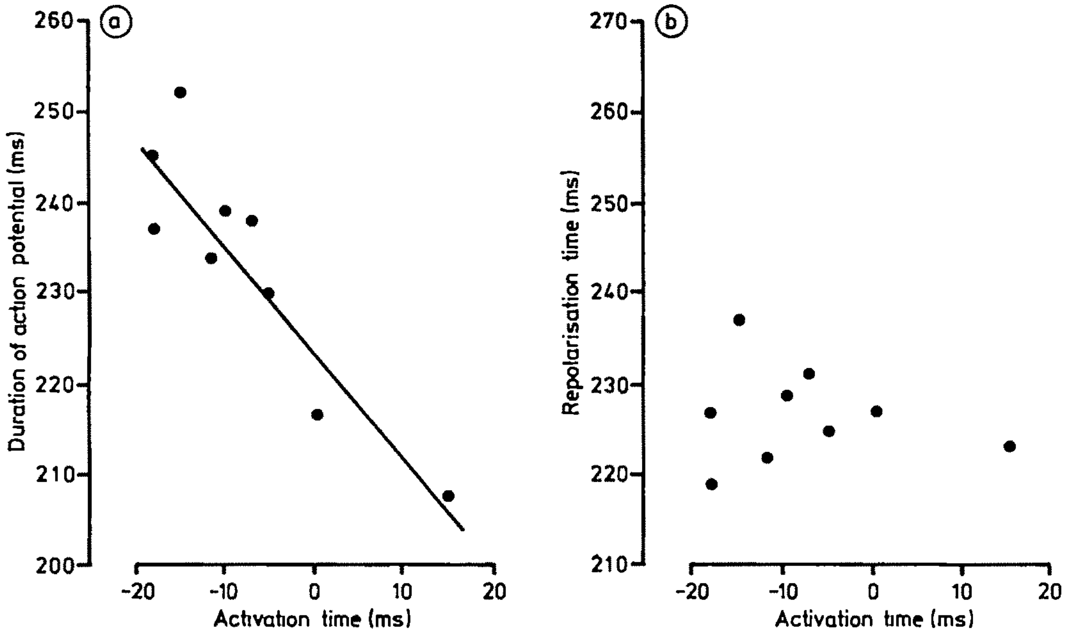

Fig 3 *Relation between the duration of the action potential and the activation time in a patient with upright T waves. The relation between the duration of the monophasic action potential and the activation time for left ventricular sites in one patient (patient 4, table 1) is given on the left. The line for the regression of the duration of the action potential on the activation time is shown (slope −1·17). The resulting distribution of repolarisation times and activation times is shown on the right.*

In view of the variation in the slopes of the regression lines in individual patients, a mean activation time, duration of action potential, and repolarisation time were derived for each site by pooling the standardised data from all 10 patients. Figure 5 shows the relation between the activation time and the duration of the action potential for these standardised site means. There was a close inverse relation between the activation time and the duration of the action potential (slope −1·44, 95% confidence limits of slope −1·15 to −1·73, p < 0·001). In contrast with the data for individual patients, a statistically significant inverse relation between repolarisation time and activation time was evident in the pooled data, indicating earlier repolarisation at sites of later activation (slope −0·44, 95% confidence limits of slope −0·15 to −0·73, p < 0·001). The fact that a statistically significant inverse relation was demonstrated in only one of the 10 patients, when considered individually, reflects the scatter of results

Table 1 *Regression of action potential duration on the activation time in patients with upright T waves*

Case No	*Correlation coefficient*	*Slope*	*95% confidence limits of slope*	*Probability*
1	−0·67	−0 97	−0·10 to −1·84	p < 0·05
2	−0·66	−1 01	+0·04 to −2·05	p < 0·10, NS
3	−0·73	−0 89	−0 06 to −1·72	p < 0 05
4	−0·89	−1 17	−0 67 to −1·67	p < 0·001
5	−0 08	−0 10	+1·01 to −1·21	p > 0·10, NS
6	−0 64	−0·90	+0·06 to −1·86	p < 0·10, NS
7	−0·73	−0·71	−0 12 to −1·30	p < 0 025
8	−0·95	−1·30	−0·93 to −1·67	p < 0 001
9	−0 67	−1·04	−0·02 to −2·06	p < 0·05
10	−0·94	−2 09	−1·35 to −2·83	p < 0 001

Table 2 *Dispersion of activation time, action potential duration, and repolarisation time in patients with upright T waves*

		Dispersion (ms)		
Case No	*No of sites measured*	*Activation*	*Action potential duration*	*Repolarisation*
1	10	28	36	31
2	9	23	48	32
3	8	34	41	22
4	9	33	44	20
5	9	19	25	28
6	9	16	21	15
7	9	31	30	20
8	10	33	37	18
9	9	20	26	26
10	8	34	89	55

The number of sites giving acceptable potentials varied between eight and 10 in different patients. The dispersion of each variable is the difference between the maximum and minimum values of that variable.

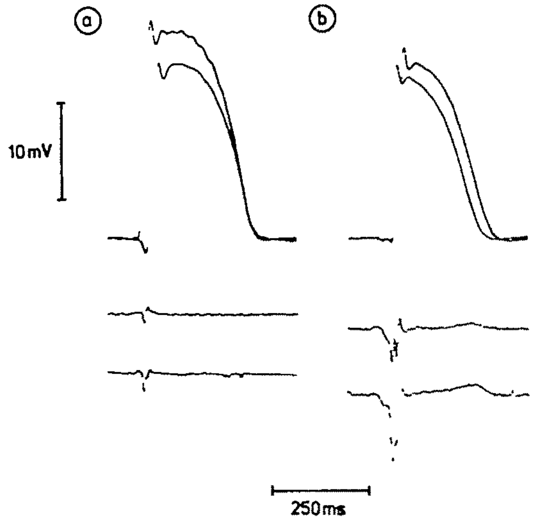

Fig 4 *(a) Monophasic potentials at two epicardial sites in a patient with upright T waves. Potentials were aligned using the reference signals (bipolar recordings, lower traces). Despite differing activation times, repolarisation time at the two sites was almost synchronous, reflecting a shorter action potential duration at the site with later activation.*
(b) Monophasic potentials at two epicardial sites in a patient with inverted T waves caused by aortic stenosis. The duration of the action potential was independent of the activation time and hence the site which activated later also repolarised later. For clarity of presentation, the upstrokes of potentials have been retouched.

within individuals and the relatively flat slope of the regression line relating repolarisation time and activation time.

The activation and repolarisation sequences derived from these individual site means are plotted schematically in fig 6. Activation occurred earliest in the anterior and posterior septum. It then spread in two general directions, from each septal border towards the free wall of the ventricle and from apex to base. Dispersion of the mean activation times over the left ventricular sites was 23 ms. The repolarisation sequence was very different from the activation sequence. Repolarisation occurred earliest in the posterobasal region—the areas of latest activation. The areas over the anterior and posterior septum were the last to repolarise; these areas correspond approximately to the earliest areas of activation. There was therefore an inverse relation between the sequences of activation and repolarisation. The dispersion of the mean repolarisation times over the left ventricle was 14 ms.

AORTIC STENOSIS WITH T WAVE INVERSION

We studied activation time, action potential duration, and repolarisation time in four patients with T wave inversion caused by aortic stenosis. In contrast with patients with upright T waves, the duration of the action potential was independent of the activation time (table 3). As a consequence, the repolarisation time was determined by the activation time (fig 4b.)

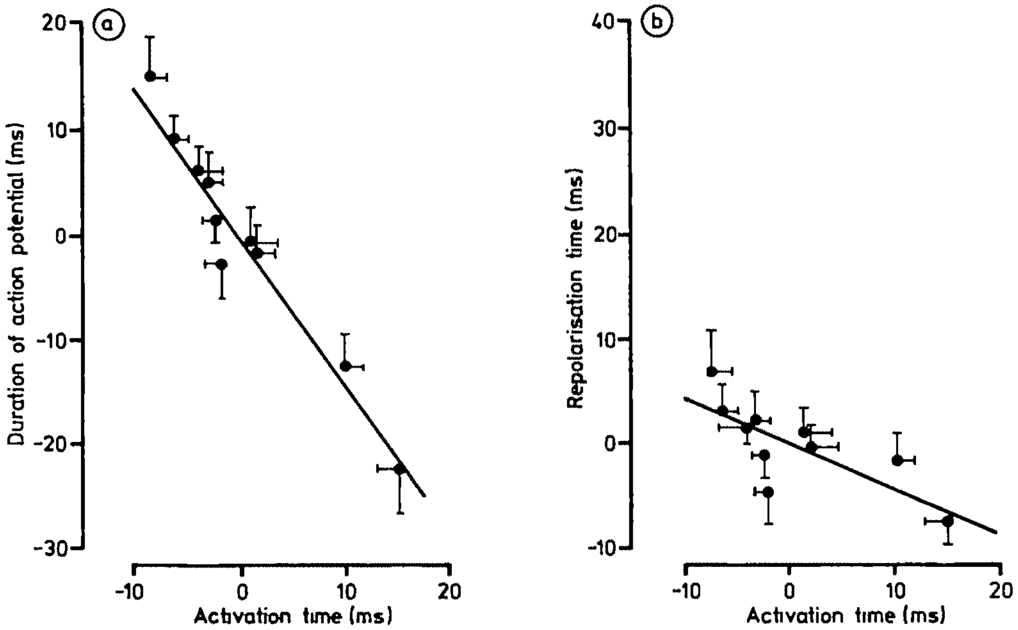

Fig 5 *Mean relation between (a) the duration of the action potential and the activation time for all 10 patients with upright T waves. Normalised data from individuals were pooled to provide a mean activation time and the mean duration of the action potential for each site. (b) The relation between repolarisation time and activation time. Both figures show the SEMs and the regression lines.*

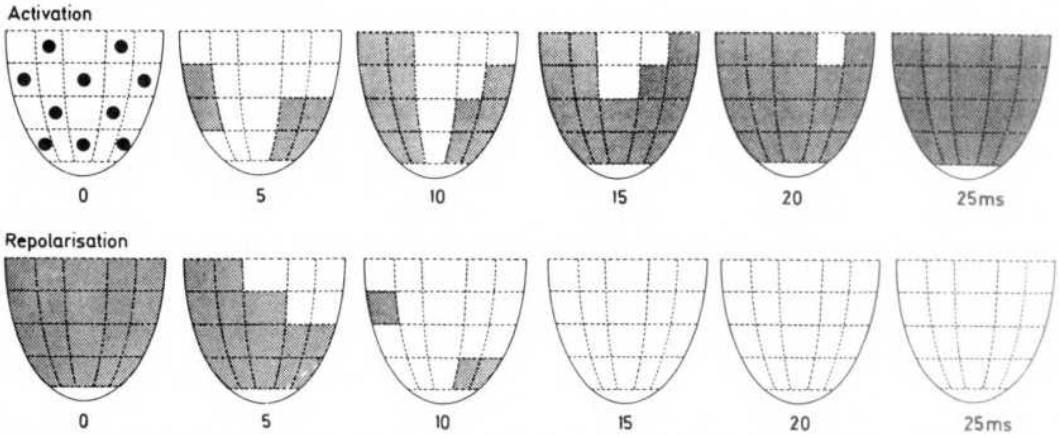

Fig 6 *Representation of left ventricular activation and repolarisation sequences for patients with upright T waves. Diagrams are based on the means of the normalised data for all 10 patients with upright T waves. The 10 mapped sites within the grid are indicated by dots. Estimates of activation time and repolarisation time at unmapped sites were derived as the mean of measurements of all adjacent sites. The shaded areas indicate the extent of depolarised myocardium in successive 5 ms timeframes, timed from the earliest activation or repolarisation. The anterior septum is on the left and the posterior on the right (as in fig 1). The dispersion of activation was 23 ms and the dispersion of repolarisation was 14 ms.*

Table 3 *Regression of action potential duration on activation time in patients with aortic stenosis*

Case No	*Correlation coefficient*	*Slope*	*95% confidence limits of slope*	*Probability*
Inverted T waves:				
1	−0·36	−0·22	+0·30 to −0·84	p > 0·10, NS
2	−0·59	−0·56	+0·04 to −1·16	p < 0·10, NS
3	−0·17	−0·21	+0·76 to −1·18	p > 0·10, NS
4	+0·06	+0·06	+0·84 to −0·72	p > 0·10, NS
Upright T waves:				
5	−0·79	−1·33	−0·48 to +2·18	p < 0·001

In three of the four patients dispersion of repolarisation time was greater than dispersion of action potential duration (table 4).

The mean activation time, action potential duration, and repolarisation time for each site were derived by pooling the standardised data for all four patients (fig 7). There was no significant relation between the action potential duration and activation time. As a result, the repolarisation time was significantly related to the activation time (slope 0·86, 95% confidence limits of slope 0·26 to 1·46, p < 0·01).

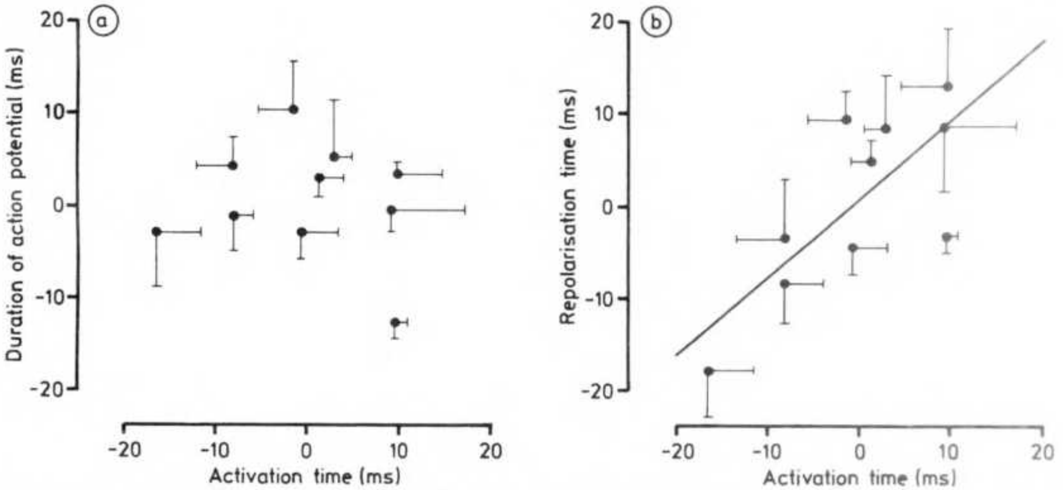

Fig 7 *Mean relation between (a) the duration of the action potential and the activation time for all four patients with T inversion caused by aortic stenosis. (b) The resultant relation between repolarisation time and activation time. Both figures show the SEMs and the regression lines.*

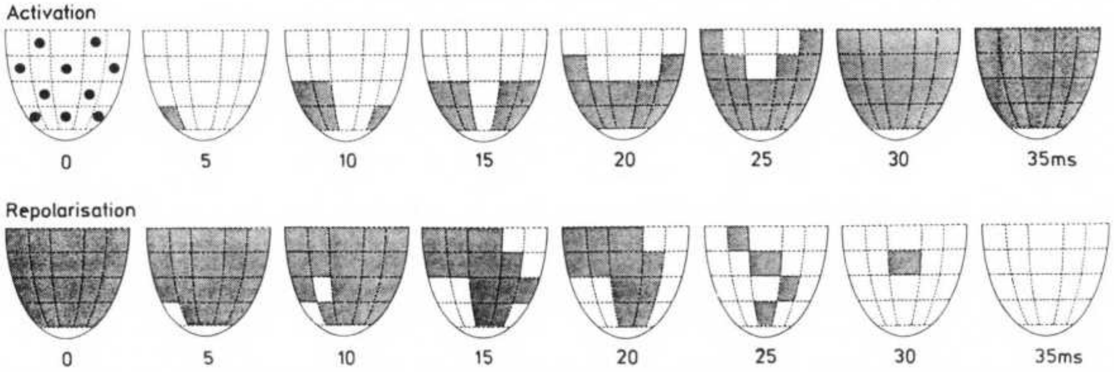

Fig 8 *Representation of left ventricular activation and repolarisation sequences for patients with T inversion caused by aortic stenosis. Diagrams are based on the means of the normalised data of the four patients. The shaded areas indicate the extent of depolarised myocardium in successive 5 ms timeframes. The dispersion of activation was 26 ms and the dispersion of repolarisation was 31 ms.*

Table 4 *Dispersion of activation time, action potential duration, and repolarisation time in patients with aortic stenosis*

		Dispersion (ms)		
Case No	*No of sites measured*	*Activation*	*Action potential duration*	*Repolarisation*
Inverted T waves:				
1	9	62	37	48
2	10	20	23	17
3	10	24	37	38
4	10	26	25	47
Upright T waves:				
5	10	35	63	39

Figure 8 shows the mean activation and repolarisation sequences. The activation sequence was similar to the sequence in patients with upright T waves. Activation occurred earliest on either side of the septum and proceeded from the septum to the free wall and from the apex to the base. Dispersion of the mean activation times was 26 ms. The repolarisation sequence differed from that in patients with upright T waves; it resembled the activation sequence. Dispersion of the mean repolarisation times (31 ms) was slightly greater than dispersion of activation times.

AORTIC STENOSIS WITH UPRIGHT T WAVES

We studied one patient with aortic stenosis and upright T waves. This patient resembled the other patients with upright T waves in showing a statistically significant inverse relation between action potential duration and activation time (table 3).

VARIATION IN THE EPICARDIAL TEMPERATURE

In the four patients we studied a two way analysis of variance showed no statistically significant difference between epicardial sites. The left ventricle was considered as a series of four coaxial rings from base

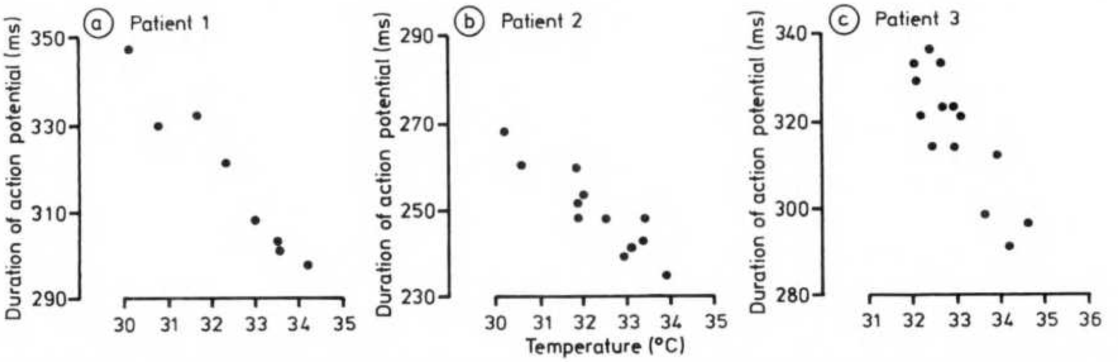

Fig 9 *Relation between the duration of the monophasic action potential and temperature. The effects of cooling on action potential duration in three separate patients are shown.*

to apex. The mean temperature of the four rings from base to apex was 35·1, 35·1, 35·0, and 34·7 °C (differences non-significant).

In three of the four patients the relative magnitude of temperature effects on action potential duration was determined by recording monophasic potentials during cooling. The action potential duration was prolonged (fig 9). The slopes of the regression lines relating action potential duration and temperature varied between 4 and 12 ms prolongation per °C of cooling.

Discussion

This study presents the first maps of the sequence of human epicardial repolarisation. We showed that epicardial repolarisation gradients do exist and that they are related to the configuration of the T wave on the surface electrocardiogram. The relation between activation and repolarisation sequences was different in patients with upright T waves and in those with inverted T waves.

STUDY LIMITATIONS

It is not feasible to record intracellular potentials from the beating whole human heart. The use of monophasic action potentials as a substitute depends on certain assumptions. Monophasic potentials are of much lower amplitude than their intracellular counterparts. Though their overall duration corresponds closely with the intracellular potentials,[8 9] the point of 90% repolarisation is measured in relation to the maximum plateau amplitude and hence may be amplitude dependent. The 90% repolarisation point is only independent of amplitude if the monophasic potential is proportionately reduced from the intracellular potential throughout the whole of repolarisation. Previous studies in isolated rabbit hearts have suggested that this is indeed the case.[9]

There are additional problems in studying repolarisation in vivo. Repolarisation, unlike activation, is a dynamic process, influenced by many factors and capable of rapid change.[7] Consequently, the "normal" or baseline repolarisation state is difficult to establish and to maintain. During open chest surgery differential epicardial cooling or cardiopulmonary bypass may cause changes in repolarisation.

We saw modest evidence of differential apical cooling. Based on the lengthening of the duration of the action potential during cooling, the observed 0·4°C temperature difference between base and apex would be expected to lengthen the action potential duration at the apex by 2–5 ms relative to the base. This effect is small compared with the observed differences in the duration of the action potential.

Cardiopulmonary bypass causes a transient prolongation of the duration of the action potential in the first minutes of bypass.[12] In the present study we started mapping after six minutes of bypass to avoid these transient effects. We adopted a strategy of repeated point mapping to ensure that comparisons between epicardial sites would be independent of any continuing time-dependent influences.

We therefore believe that intraoperative influences on epicardial repolarisation gradients were relatively small.

DISPERSION OF REPOLARISATION

In patients with upright T waves we found an inverse relation between the duration of the action potential and the activation time. The slope of this relation was significantly more negative than −1, reflecting inverse activation and repolarisation sequences. A similar inverse relation between the duration of the action potential and the activation time was reported by Franz *et al*, who recorded endocardial monophasic action potentials in seven patients and epicardial potentials in three patients.[10]

By contrast, in patients with T wave inversion caused by aortic stenosis the duration of the action potential was independent of the activation time (table 3). As a result the repolarisation sequence was largely determined by the activation sequence. Differing relations between the activation and repolarisation sequences of patients with upright and inverted T waves have been reported before.[13]

An important consequence of the observed inverse relation between the duration of the action potential and the activation time is a reduction in the dispersion of repolarisation. In patients with upright T waves, the dispersion of the repolarisation time was less than the dispersion of duration of the action potential. By contrast, in patients with T inversion caused by aortic stenosis, in whom the duration of the action potential was independent of the activation time, dispersion of repolarisation time was greater than that of the duration of the action potential.

Dispersion of repolarisation has been shown to favour the development of arrhythmias,[4-6] so minimising dispersion may be a protective mechanism. The observed inverse relation between the activation time and the duration of the action potential may therefore represent a fundamental intrinsic antiarrhythmic property of the myocardium.

DIFFERENCES IN EPICARDIAL REPOLARISATION AS DETERMINANTS OF T WAVE CONFIGURATION

The concordance of QRS and T waves in the surface electrocardiogram led to the classic hypothesis that activation and repolarisation must proceed in opposite directions.[14] Such an inverse relation might result from a transmural endocardial-epicardial gradient, from gradients across the epicardial surface, or from both.

There is a consensus, from animal studies, that transmural activation and repolarisation gradients are opposite.[15 16] Whereas activation proceeds from endocardium to epicardium, repolarisation proceeds from epicardium to endocardium. Franz *et al* have provided evidence of a similar transmural gradient in man, based on the finding that endocardial repolarisation occurs later, in relation to the QT interval of the surface electrocardiogram, than epicardial repolarisation.[10]

For gradients across the epicardial surface the situation is less clear. There is some measure of agreement that refractory periods[17] and action potentials[18] are longer at the apex than at the base. Abildskov found that on the epicardium recovery from refractoriness resembled the activation sequence, whereas there was an inverse relation on the endocardium.[19] Toyoshima *et al* found differing relations between activation and repolarisation on the anterior and posterior epicardial surfaces.[20] Spach and Barr found that the apex repolarised later than the base,[15] hence suggesting an inverse relation between activation and repolarisation.

In the present study, we have found that the repolarisation wavefront in individual patients is complex, reflecting differences in repolarisation times between closely adjacent areas of epicardium. A similar complexity of the repolarisation wavefront has been reported in animals.[18 21] Pooling data between patients showed that activation and repolarisation sequences were opposite—activation proceeded from septum to free wall and from apex to base, whereas repolarisation proceeded from base to apex and from free wall to septum. By contrast, in patients with T inversion, the repolarisation sequence broadly resembled the activation sequence. These findings are consistent with classic theories of the genesis of T waves.They suggest that the normal concordance of QRS and T waves is the result of the observed inverse relation between the duration of the action potential and the activation time.

For ethical reasons, our study was confined to the epicardium and simultaneous endocardial recordings were not undertaken. The relative contribution of epicardial and transmural gradients to the T wave remains uncertain. Earlier estimates of dispersion of repolarisation in man, which were based on the variation in QT interval over the body surface, range from 60 to 80 ms in normal subjects.[22 23] These values are considerably greater than the epicardial dispersion we found. This suggests that transmural gradients have a large effect in the overall dispersion of repolarisation.

THE LINK BETWEEN THE DURATION OF THE ACTION POTENTIAL AND THE ACTIVATION TIME

The simplest explanation for the inverse relation between the duration of the potential and the activation time is an indirect association through a third factor, such as site. A posterobasal location, for example, might predetermine both a short action potential duration and a late activation time. The question would then be restated as to how activation time and the duration of the action potential might be jointly predetermined on a regional basis.

Alternatively, there may be a direct causal relation, such that the duration of the action potential adapts directly to the activation sequence. Although the basis for such adaptation is unclear, there is indeed evidence that the duration of the action potential can alter in response to changes in the activation sequence. Alteration in the ventricular activation sequence, whether caused by ventricular pacing,[24 25] intermittent left bundle branch block,[26 27] or intermittent pre-excitation[28] can produce T wave changes that persist after the restoration of normal activation. By inference, the duration of the action potential alters during the period of abnormal activation, resulting in an abnormal repolarisation sequence when normal activation is restored. It can be postulated that an intrinsic property of the myocardium enables the duration of the action potential to adapt to its activation sequence. This would result in a direct link between the duration of the action potential and the activation time and this would provide a possible mechanism for the inverse relation that we found.

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Effect of propranolol on the QT intervals of normal individuals during exercise: a new method for studying interventions

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SUMMARY A new method was used to study the effect of a single dose of propranolol on the QT intervals during exercise in 11 normal volunteers. They exercised maximally on a bicycle ergometer and repeated the test after taking propranolol (40 mg) by mouth two hours before. Electrocardiograms were continuously recorded on magnetic tape and the cardiac cycle length (RR interval) and the QT interval were measured every five seconds by a computer aided method. The RR-QT data from each test during the exercise phase were analysed by an exponential formula, $QT = A - B \times \exp(-k \times RR)$ and by Bazett's formula, $QT = K \times \sqrt{(RR)}$. Three reference QT intervals, QT_{c1}, QT_{c2}, and QT_{c3}, estimated at RR = 400, 700, and 1000 ms respectively from the regression curves of both formulas were compared. The exponential formula, which consistently gave a better fit with the data, showed that propranolol had a biphasic action on the QT intervals during exercise. It significantly prolonged the mean (SD) interval at longer cycle lengths (from 287 (27) to 305 (18) ms at RR = 1000 ms and shortened it at shorter cycle lengths (from 198 (14) to 179 (16) ms at RR = 400 ms). In contrast, Bazett's formula did not show any significant effect when the same raw data were used.

The exponential formula can be adapted to study other interventions or conditions that affect QT intervals.

The results of previous studies of the effect of propranolol on the QT interval are contradictory. Milne *et al* showed that intravenous propranolol prolonged the QT interval at identical atrial paced cycle lengths,[1] whereas Browne *et al* found no significant changes under similar conditions[2]; however, the use of Bazett's formula[3 4] shortened the rate corrected QT interval calculated from both studies. Other studies of propranolol also suggested that the QT interval corrected for heart rate by Bazett's formula was usually shortened.[5 6]

We found that the functional dependence of the human QT interval on the cardiac cycle length (RR interval) during exercise and cardiac pacing was well expressed by an exponential formula.[7] We used this exponential formula to evaluate the effects of propranolol on the QT intervals of normal individuals during exercise and we compared the results with an analysis of the same data by Bazett's formula.

Patients and methods

Eleven healthy volunteers (six men and five women, mean (SD) age 34 (7) years (range 20–48)) exercised maximally on a bicycle ergometer. They exercised once without medication after an overnight fast, and seven to 10 days later they exercised again after taking 40 mg of propranolol by mouth two to three hours before the test. This dose slowed the heart rate and caused visible symptoms of tiredness in all the volunteers, none of whom had taken propranolol before. For each test, the initial exercise load was set at 50 W and was increased in steps of 25 W every two minutes. Electrocardiographic leads I, aVF, and V5 were continuously recorded on an analogue tape recorder (Model HP3964A, Hewlett-Packard, Palo

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Alto, CA) that was started three minutes before exercise. This study protocol was approved by our institutional review board. Each person signed a form giving informed consent.

The RR and QT intervals were measured automatically every five seconds by a programmable waveform analyser (Model 3001, Norland, Fort Atkinson, WI) and the data were transmitted to an IBM-PC/AT microcomputer (IBM Personal Computer Division, Boca Raton, FL) over an IEEE-488 interface. The QT interval was measured from the beginning of the QRS complex to the apex of the T wave. In eight people in whom the end of the T wave could be clearly identified throughout the exercise the average interval from apex T to end T (eT-aT interval) was measured at rest and peak exercise. The end of the T wave was taken as the point at which the line drawn through the steepest portion of the terminal limb of the T wave cut the isoelectric line defined by the PQ segment.[8]

The RR-QT data during the exercise phase were fitted to the exponential formula[7]: $QT = A - B \times \exp(-k \times RR)$, where the parameters A, B, and k were estimated by non-linear regression with the *ASYST* scientific system (Macmillan Software, New York, NY). For comparison, the exercise RR-QT plots were also fitted to Bazett's formula[3]: $QT = K \times \sqrt{(RR)}$, in which the parameter K was estimated by linear regression. The measurements made during the recovery phase were not included in the analysis, to avoid the effects caused by QT hysteresis.[8]

DATA ANALYSIS

We compared the three reference QT intervals, QT_{c1}, QT_{c2}, and QT_{c3}, estimated from the individual regression curves at RR = 400, 700, and 1000 ms, respectively, in the control and propranolol groups. These estimates may be regarded as corrected QT intervals (see the Appendix). They are expressed as functions of the regression equations as follows:

$$QT_{c1} = A - B \times \mathrm{Exp}(-k \times 400)$$
$$QT_{c2} = A - B \times \mathrm{Exp}(-k \times 700)$$
$$QT_{c3} = A - B \times \mathrm{Exp}(-k \times 1000),$$

where the QT_c intervals are expressed in ms. A set of three QT_c intervals are required to characterise uniquely each exponential RR-QT curve. We chose the corrected QT intervals for statistical comparisons because this permits the drug induced changes in the QT_c estimates to be interpreted in terms of prolongation or shortening of QT intervals in the observable range of cycle lengths. Similar estimates of the QT_cs derived from Bazett's (or any other) formula can be compared with the values derived from the exponential formula.

The corrected QT intervals at RR = 400, 700, and 1000 ms according to Bazett's formula were estimated by the following equations:

$$QT_{c1} = K \times \sqrt{(400)}$$
$$QT_{c2} = K \times \sqrt{(700)}$$
$$QT_{c3} = K \times \sqrt{(1000)},$$

where the QT_c intervals are also expressed in ms. QT_{c3} corresponds to the conventional corrected QT interval. Zipes recently suggested that when the effects of drugs or other interventions are being evaluated the original Bazett's formula, $QT = K \times \sqrt{(RR)}$, where the K value is derived from a regression analysis, is superior to the commonly applied formula, $QT_c = QT/\sqrt{(RR)}$.[9] The relation between the two formulas is explained in the Appendix.

We compared matched sets of control and propranolol treatment values of QT_{c1}, QT_{c2}, and QT_{c3} by the one sample Hotelling T^2 test for overall differences and differences among individual pairs of QT_cs by a paired *t* test. We used the same method to analyse the corrected QT intervals obtained by Bazett's formula. *BMDP Statistical Software* (Los Angeles, CA) was used for the statistical analysis.

Results

Table 1 summarises the main results. Cardiac cycle lengths at rest and peak exercise were significantly prolonged after propranolol. Systolic blood pressure at rest and peak exercise was significantly reduced. There were no pronounced changes in diastolic blood pressures. As expected, none of the subjects showed any abnormalities during exercise or recovery. The QRS configuration was unchanged during exercise and between tests. The QRS duration remained less than 5 ms throughout the study. The average duration of exercise was not signifi-

Table 1 *Summary of results (mean (SD)) obtained from 11 volunteers who exercised under control conditions and after propranolol*

Measured variable	*Control*		*Propranolol*		*p (pair)*
CCL resting (ms)	869	(151)	1174	(168)	<0·001
CCL peak exercise (ms)	334	(23)	444	(44)	<0·001
Systolic BP resting (mm Hg)	106	(11)	99	(11)	<0·05
Diastolic BP resting (mm Hg)	70	(7)	68	(9)	NS
Systolic BP peak (mm Hg)	159	(19)	141	(24)	<0·01
Diastolic BP peak (mm Hg)	75	(12)	75	(11)	NS
Exercise duration (min)	11·1	(2·5)	10·3	(2·7)	NS
QT_{c1} (exponential) (ms)	198	(14)	179	(16)	<0·002
QT_{c2} (exponential) (ms)	257	(16)	271	(17)	<0·001
QT_{c3} (exponential) (ms)	287	(27)	305	(18)	<0·01
QT_{c1} (Bazett) (ms)	196	(13)	198	(13)	NS
QT_{c2} (Bazett) (ms)	259	(17)	261	(17)	NS
QT_{c3} (Bazett) (ms)	309	(20)	312	(20)	NS

BP, blood pressure; CCL, cardiac cycle length

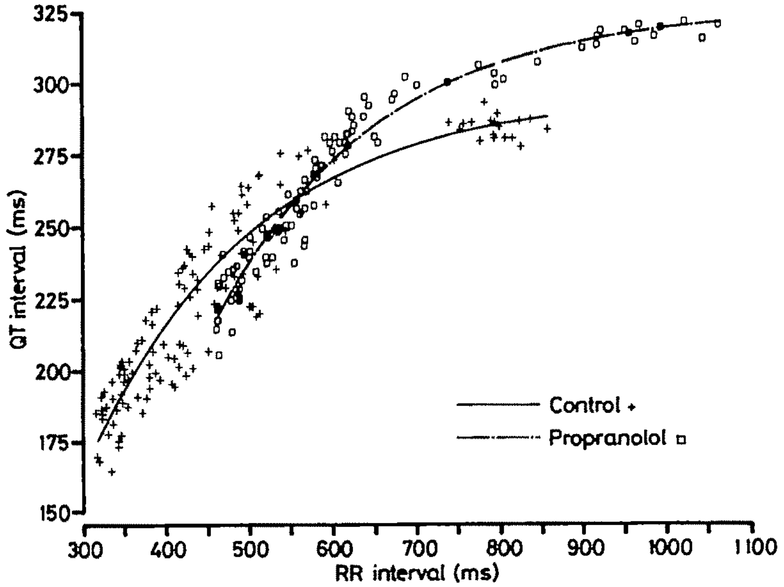

Fig 1 *A typical plot showing the RR-QT relation during exercise before (+) and after (O) propranolol together with the fit of the regression line with the exponential formula. The apparent gap in the data points on the control curve represents a rapid shortening of cycle length during the early part of exercise. Propranolol typically caused more gradual RR shortening, resulting in a more uniform distribution of data points.*

cantly altered by propranolol treatment, although all the volunteers found it harder to exercise after taking the drug.

Figure 1 shows typical plots of RR versus QT and their regression lines obtained with and without propranolol treatment in one volunteer.

Table 1 shows that there were significant differences between the control and treatment values for corrected QT intervals obtained with the exponential formula (QT_{c1}, QT_{c2}, QT_{c3}) ($p < 0.002$, Hotelling T^2 test); after propranolol QT_{c1} was significantly shortened and QT_{c2} and QT_{c3} were significantly prolonged. Figure 2 shows the QT_c changes in individual volunteers. In contrast with the exponential formula, the corrected QT intervals obtained with Bazett's formula failed to show any significant difference between the control and treatment values (table 1), although the same raw data were used in both calculations. Figure 3 compares the curves obtained with the exponential and Bazett's formulas for the exercise data used in fig 1. The exponential formula gave a consistently better fit with the observed data.

The changes in the T wave configuration during exercise were similar under control conditions and after propranolol treatment. The average (SD) eT-aT intervals measured in eight volunteers at rest were 149 (17) ms for control and 145 (14) ms after propranolol (p = NS). The values at peak exercise were 124 (22) for control and 125 (15) after propranolol (p = NS). Thus the Q-aT and Q-eT intervals showed parallel behaviour in this study.

To assess whether the RR-QT relation is dependent on the exercise protocol, we studied a separate group of five normal volunteers (three men, two women; age 22 (5)) who exercised maximally on a bicycle ergometer (50 W initial load with 25 W increases every two minutes) and a treadmill (Bruce protocol) on different days in a random order. The results (table 2) show that the RR-QT relation during the exercise phase is highly reproducible and independent of the exercise protocol.

Discussion

The present study evaluated the effects of a single oral dose of propranolol (40 mg) on the RR-QT relation in normal individuals. The effects on resting and exercise heart rate and blood pressure showed evidence of β blockade, albeit incomplete. Under these conditions the results presented in this report clearly show a biphasic effect of propranolol on the

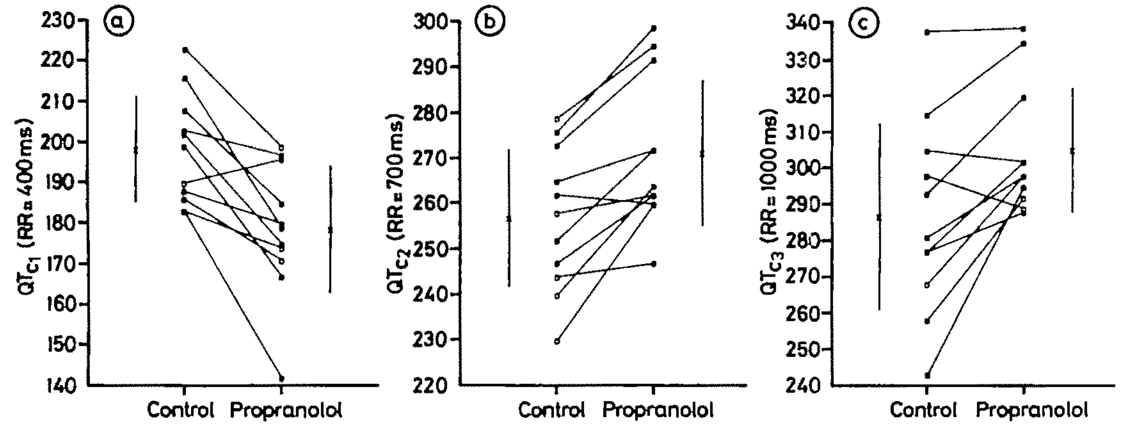

Fig 2 *Effect of propranolol on the individual (a) QT_{c1} intervals estimated at RR = 400 ms, (b) QT_{c2} intervals estimated at RR = 700 ms, and (c) QT_{c3} intervals estimated at RR = 1000 ms. The mean (SD) values for each group are shown. Propranolol had a biphasic effect, shortening QT_{c1} ($p < 0{\cdot}002$) but prolonging QT_{c2} ($p < 0{\cdot}001$) and QT_{c3} ($p < 0{\cdot}01$).*

exercise QT intervals, with net prolongation at rest and shortening at peak exercise. The high reproducibility of the exercise RR-QT curves and their apparent independence of the exercise protocol indicate the reliability of the results. Milne *et al* found that propranolol causes a uniform QT prolongation over a wide range of identical paced cycle lengths.[1] This finding, taken together with the present results, suggests that a normal tendency of propranolol to prolong the QT interval is opposed by a competing mechanism during exercise. Others have shown that pretreatment of normal individuals with propranolol increases their peak concentrations of plasma potassium and catecholamine during exercise.[10-13] It was suggested that β_2 receptor mediated effects in the exercising muscles may cause the observed hyperkalaemia. An increased extracellular potassium concentration, which is known to shorten the action potential duration in the ventricular muscle,[14] might have resulted in the relative shortening of the QT interval at peak exercise.

The measurement of QT interval to the apex of the T wave rather than to its end is justified in the present study because the changes in the T wave configuration during exercise did not contribute to the differences between the control and propranolol treated conditions. Under these conditions it is better to use the Q-apexT interval which can be measured more accurately.[15]

Propranolol is used in the treatment of long QT syndrome[16] and is known to increase the otherwise low variability of the QT interval during exercise in those patients.[17] It is interesting to note that propranolol also increases the responsiveness of QT intervals in normal subjects through the biphasic effect.

Though Bazett's formula is simpler to use, it is inappropriate for the study of QT intervals during exercise. Mathematically, two regression curves constructed by Bazett's formula cannot cross each other, except at the origin, irrespective of the nature of the data sets. Thus it is theoretically impossible to demonstrate the rate dependent biphasic effect of propranolol on the exercise QT interval by Bazett's formula (fig 3).

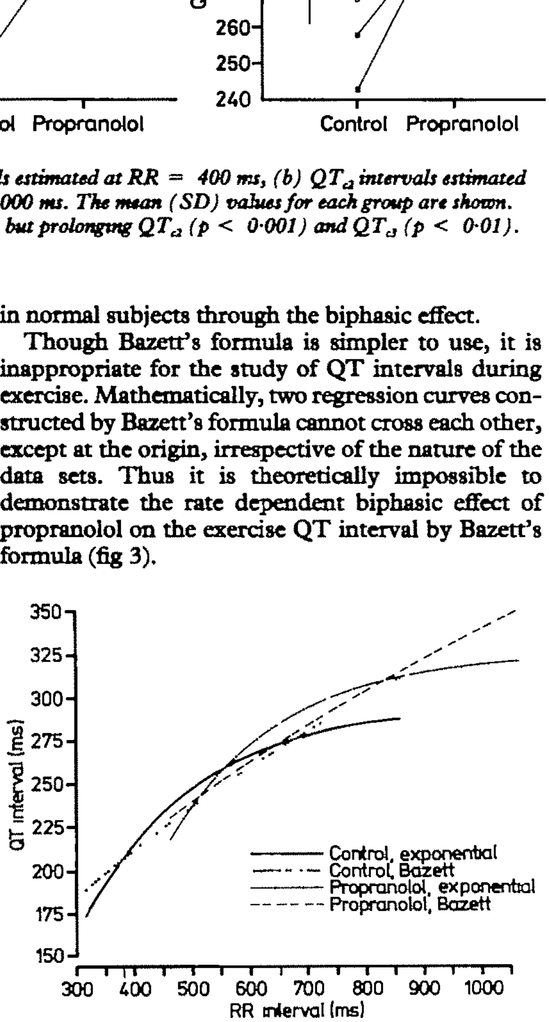

Fig 3 *Comparison of the fit of the exponential and Bazett formulas with the RR-QT data shown in fig 1. The regression curves for Bazett's formula deviated markedly from the data points and showed very little change after propranolol administration. Bazett's curves are mathematically precluded from intersecting except at the origin.*

Table 2 *Reproducibility of QT_c parameters in five normal individuals who exercised on bicycle and treadmill on different days in a random sequence*

No	*Exercise type*	*Exercise duration (min)*	*QT_{c1} (ms)*	*QT_{c2} (ms)*	*QT_{c3} (ms)*
1	Bicycle	9·1	197	272	307
	Treadmill	14·0	198	269	309
2	Bicycle	10·0	198	266	304
	Treadmill	13·0	195	263	302
3	Bicycle	10·0	189	256	285
	Treadmill	14·0	192	248	277
4	Bicycle	16·0	199	266	295
	Treadmill	15·0	199	267	299
5	Bicycle	12·0	188	252	281
	Treadmill	13·4	191	257	287
Mean (SD)	Bicycle	11·4 (2·5)	194 (5)	262 (8)	294 (11)
Mean (SD)	Treadmill	13 9 (0 7)	195 (4)	260 (8)	294 (13)
p		NS	NS	NS	NS

QT_{c1}, QT_{c2}, and QT_{c3} were estimated according to the exponential equations given in the text.

IMPLICATIONS

The present study offers a general method for studying the effects of various interventions on the dynamic behaviour of the QT interval. The concept of corrected QT (QT_c) interval has been extended to be applicable to any RR-QT formula. In the case of the exponential formula, QT_c may be regarded as a three dimensional vector with QT_{c1}, QT_{c2}, and QT_{c3} as its components. Other important features of the method include the analysis of individual RR-QT curves without prior pooling, and use of computer aided measurement of time intervals to collect accurately large numbers of data points, all of which contribute to the QT_c estimates. The results presented here offer convincing evidence that the method is sensitive enough to detect subtle, but potentially important, changes in QT intervals caused by interventions. We suggest that this method should be adopted in future investigations, under appropriate conditions.

We thank our summer students Azhil Durairaj and Edward G Gillan for their help in data collection and analysis.

Appendix

GENERALISED DEFINITION OF THE CORRECTED QT (QT_c) INTERVAL

To extend the concept of QT_c to formulas other than Bazett's, we first need to define QT_c in general terms as follows:

If the dependence of the QT interval on the cardiac cycle length is represented by the equation

$$QT = f(RR) ,$$

where f(RR) is a known function of the RR interval, then QT_c is, by definition, given by

$$QT_c = f(RR_r) ,$$

where RR_r is a reference cycle length chosen such that f(RR) gives consistent results for RR = RR_r. For practical reasons RR_r should be chosen within the expected physiological range of RR. It is possible to define more than one QT_c by assigning different values to RR_r. This feature is essential for the multiparameter formulas, as explained later.

APPLICATION TO BAZETT'S FORMULA

Bazett's formula is written as: $QT = K \times \sqrt{(RR)}$. Application of the above definition yields: $QT_c = K \times \sqrt{(RR_r)}$. From these two equations we get:

$$K = \frac{QT_c}{\sqrt{(RR_r)}} = \frac{QT}{\sqrt{(RR)}} .$$

Now, if RR is expressed in seconds and RR_r is set to 1 s, we get the popular equation:

$$QT_c = \frac{QT}{\sqrt{(RR)}} ,$$

which was first given by Taran and Szylagyi[4] without a clear mathematical explanation. The general definition given above, however, is consistent with the conventional definition of QT_c.

APPLICATION TO THE EXPONENTIAL FORMULA

According to the general definition, the QT_c for the exponential formula is given by:

$$QT_c = A - B \times \exp(-k \times RR_r) .$$

Unlike Bazett's formula, however, the exponential formula requires three QT_c values defined at three well spaced RR_r values, to characterise uniquely each exercise curve. These QT_c values may be defined as

$$QT_{ci} = A - B \times \exp(-k \times RR_{ri}) ,$$

where RR_{ri} = 400, 700, and 1000 ms for i = 1, 2, and 3 respectively. This particular set of RR_{ri} values is suitable for comparing exercise RR-QT curves. The curves can be reconstructed from the above set of QT_{ci} parameters by use of the well known Newton-Raphson recursion algorithm[18] to solve for A, B, and k. Thus QT_{ci} and the model parameters (A, B, k) contain the same information on the RR-QT curves. The former set is preferred, however, because the changes in QT_{ci} are easier to interpret in physiological terms.

In order to use multiparameter formulas, there must be some way to change the RR interval over an appropriate range to obtain reliable estimates of the model parameters. With narrow RR interval ranges, the influence of measurement and rounding errors may render the parameter estimates unreliable. Cardiac pacing and exercise provide non-pharmacological means of producing a sufficiently wide range of RR intervals under fairly controlled conditions. Autonomic tests such as the Valsalva manoeuvre and cold pressor treatment may also be applied, but the RR changes tend to be relatively narrow and therefore higher precision in the RR and QT measurements may be required.

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Assessment of the thickness of the right ventricular free wall by magnetic resonance imaging in patients with hypertrophic cardiomyopathy

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SUMMARY Electrocardiogram gated magnetic resonance imaging was performed in nine healthy volunteers, in four patients with pulmonary hypertension, and in 16 patients with hypertrophic cardiomyopathy. Fifty two short axis images in diastole were examined to assess the usefulness of magnetic resonance imaging for the measurement of the thickness of the free wall of the right ventricle and the degree of hypertrophy of the right ventricular free wall in hypertrophic cardiomyopathy and pulmonary hypertension. Magnetic resonance imaging gave a clear image of 68% of the length of the right ventricular free wall, showing both the endocardial and epicardial margins. The mean (1 SD) thickness of the right ventricular free wall measured at a total of 512 points was 0·44 (0·12) cm in patients with hypertrophic cardiomyopathy, 0·29 (0·08) cm in healthy individuals, and 0·73 (0·27) cm in patients with pulmonary hypertension.

Electrocardiogram gated magnetic resonance imaging is a useful method for the non-invasive evaluation of the left ventricle,[1 2] left atrium, thoracic aorta,[3] and pericardium.[4] It has also been used to estimate the thickness of the wall of the left ventricle.[5 6] There are several reports of the measurement of the thickness of the free wall of the right ventricle by echocardiography,[7-9] but only one by magnetic resonance imaging.[10] We have assessed whether magnetic resonance imaging can be used to measure the right ventricular free wall, particularly in patients with hypertrophic cardiomyopathy.

Patients and methods

PATIENTS

We studied 16 patients with hypertrophic cardiomyopathy, four patients with pulmonary hypertension (right ventricular systolic pressures > 70 mm Hg), and nine healthy volunteers. In all the patients the diagnosis was based on M mode and cross sectional echocardiography[11-13]; cardiac catheterisation was performed in those with hypertrophic cardiomyopathy (table 1)

MAGNETIC RESONANCE IMAGING

We used an electrocardiogram gated saturation recovery spin echo pulse sequence for imaging on a Magnetom (1·5 tesla). Imaging was triggered by the middle point of the R wave upstroke. The echo time was 34 ms, and all the images were obtained 74 ms after the triggering point. We used this timing for end

Table 1 *Acquisition of data in healthy volunteers and patients*

	Short axis image			*Long axis image*		
Group	*No*	*Images*	*Points*	*No*	*Images*	*Points*
Healthy	9	16	159	5	5	28
HC	16	31	303	8	8	37
PH	4	5	50	0	0	0
Total	29	52	512	13	13	65

HC, hypertrophic cardiomyopathy; PH, pulmonary hypertension.

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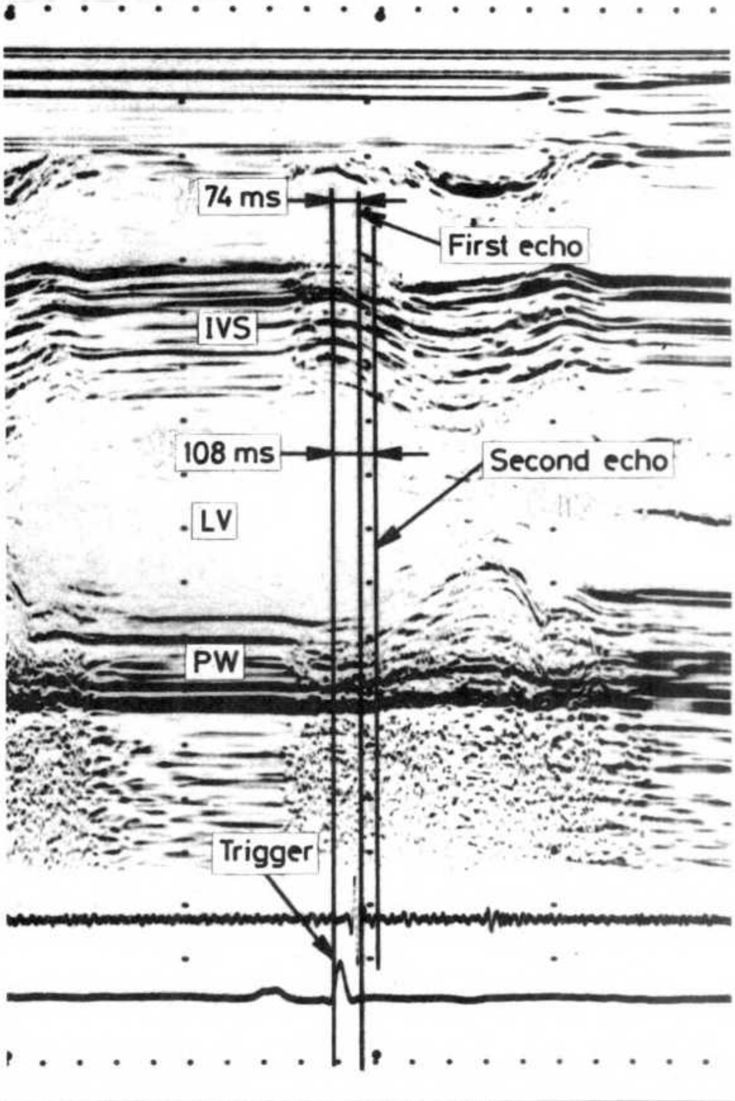

Fig 1 *M mode echocardiogram showing timing (74 ms after trigger) of the first echo image, which was used for end diastolic measurements. IVS, interventricular septum; LV, left ventricle; PW, posterior wall of the left ventricle.*

diastolic measurements because the timing occurs almost simultaneously with the start of ventricular mechanical contraction (fig 1). The reconstruction matrix was 256 × 256 with spatial resolution of 0·16–0·20 cm. Each cross sectional image was reconstructed for 512–1024 cardiac cycles by a two dimensional Fourier transformation technique. We obtained a long axis image of the left ventricle in the coronal plane in the right anterior oblique position (fig 2b). The degrees were determined individually in the transaxial planes. Then, with the patient in the oblique position, we rotated the gradient angle to obtain the short axis image in the paraxial plane (fig 2d), which was perpendicular to the long axis of the left ventricle; this image was used for the measurements. In 13 of 29 cases we obtained a long axis image (fig 2c), that showed the right ventricular free wall. The dual measurements in these individuals permitted us to evaluate the variability in the measurements of the wall thickness in these two

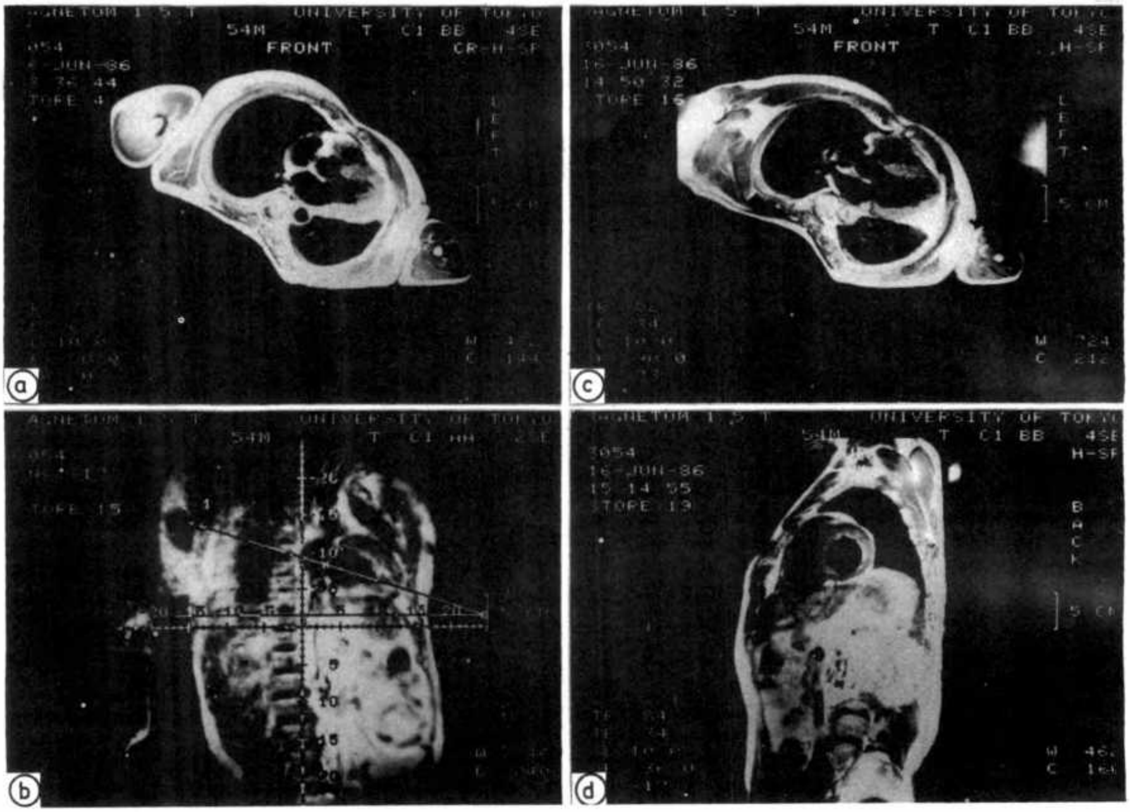

Fig 2 *Methods for obtaining short axis image of the heart. (a) Transaxial image obtained in right anterior oblique position so that the coronal plane includes the left ventricular long axis. (b) Long axis image in the coronal plane. (c) Long axis image perpendicular to the image in the coronal plane. This image included the right ventricular free wall and was used to measure the wall thickness and to evaluate variability in measurements from different views. (d) Short axis image in the paraxial plane perpendicular to the coronal plane and to the left ventricular long axis. This image was used for all measurements.*

views.

MEASUREMENTS

We measured the thickness of the right ventricle at centimetre intervals along the wall of the zone with clearly defined endocardial and epicardial margins (fig 3). In each image we measured the length of the free wall and the length of the zone with clearly defined margins. Then we summed the lengths of the free wall and the lengths of the zone with clear margins of all images for each group and calculated the ratio of the zone with clear margins to the length of the free wall. In addition, we measured the maximum and minimum thickness of the free wall and the maximum thickness of the interventricular septum in each image.

CROSS SECTIONAL ECHOCARDIOGRAPHY

In 19 individuals we measured the thickness of the right ventricular free wall by cross sectional echocardiography within a few days of the magnetic resonance imaging study. The results of both studies were compared.

VARIABILITY OF MEASUREMENTS FROM DIFFERENT VIEWS

On the long axis images, the thickness of the free wall of the right ventricle was measured every centimetre in the zone with clearly defined margins. The results were compared with measurements on the short axis images.

STATISTICAL ANALYSIS

All results were expressed as the mean (1 SD). Differences between two groups were tested by Student's unpaired *t* test and differences among three groups were analysed by one way analysis of variance. The degree of agreement between the results of measurements made by magnetic resonance imaging with those made by cross sectional

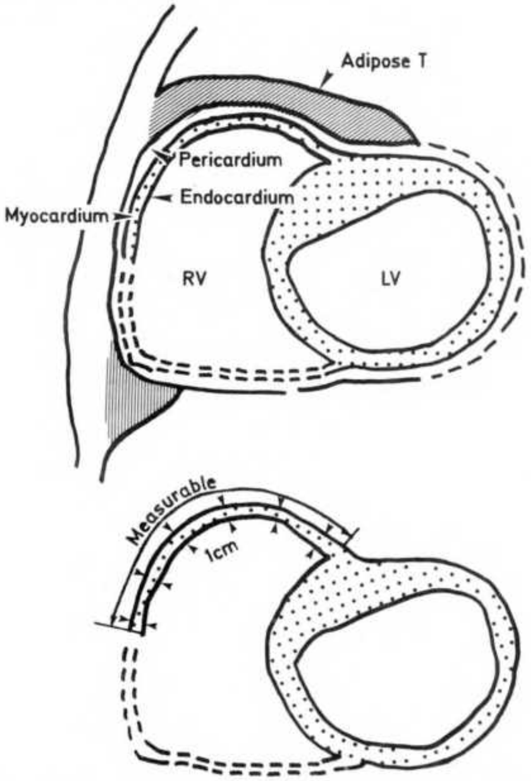

Fig 3 *Diagram of the anatomical structures surrounding the right ventricular free wall (upper panel) and the methods of measuring the thickness (lower panel). Wall thickness was measured every 1 cm where the endocardial and epicardial margins were clearly defined. LV, left ventricle; RV, right ventricle.*

echocardiography was assessed by the method of Bland and Altman.[14]

Results

In the 16 patients with hypertrophic cardiomyopathy we obtained 31 short axis images and we measured the thickness of the free wall at 303 points (figs 4 and 5, table 1). The corresponding figures for the nine normal volunteers and four patients with pulmonary hypertension were 16 and five images and 159 and 50 points respectively (figs 6 and 7, table 1).

RATIOS

The ratios of the length of the zone with clearly defined margins to the length of the right ventricular free wall were 0·65 (163·8 cm/251·6 cm) in healthy volunteers, 0·71 (311·2 cm/439·6 cm) in patients with hypertrophic cardiomyopathy, 0·63 (50·7 cm/81·1 cm) in patients with pulmonary hypertension, and 0·68 (525·7 cm/772·3 cm) in the total study group. Magnetic resonance imaging enabled us to measure the thickness of 68% of the length of the right ventricular free wall.

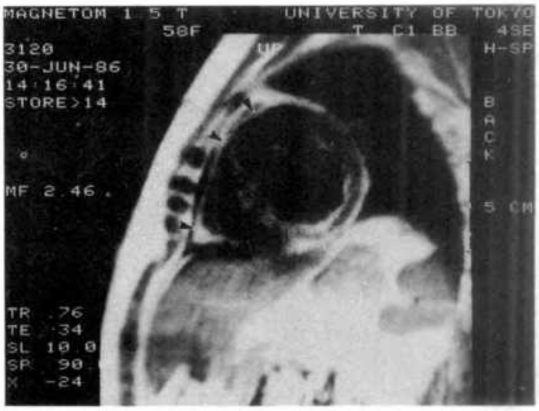

Fig 4 *A cross sectional image in a patient with hypertrophic cardiomyopathy with obstruction of the left and right ventricular outflow tracts. Arrows indicate the free wall of the right ventricle. Where the endocardial and epicardial margins of the right ventricle were clearly distinguishable the thickness of the free wall was measured every 1 cm.*

COMPARISON OF MAGNETIC RESONANCE IMAGING WITH CROSS SECTIONAL ECHOCARDIOGRAPHY

The mean difference (d) between the measurements obtained by the two methods was −0·04 cm and its standard deviation (s) was 0·06 cm. The standard errors of d and of (d–2s) were 0·01 cm and 0·02 cm respectively. The value of the appropriate point of

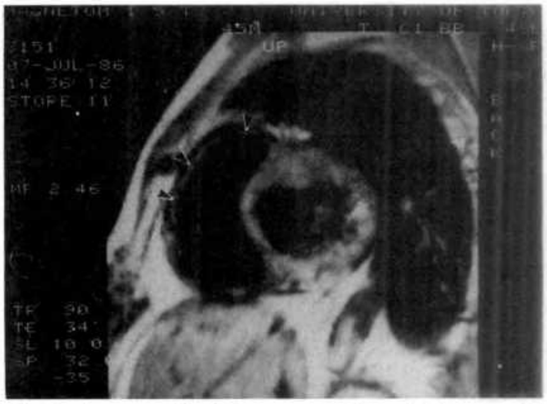

Fig 5 *A cross sectional image in a patient with hypertrophic cardiomyopathy without left and right ventricular outflow obstructions. Arrows show the free wall of the right ventricle.*

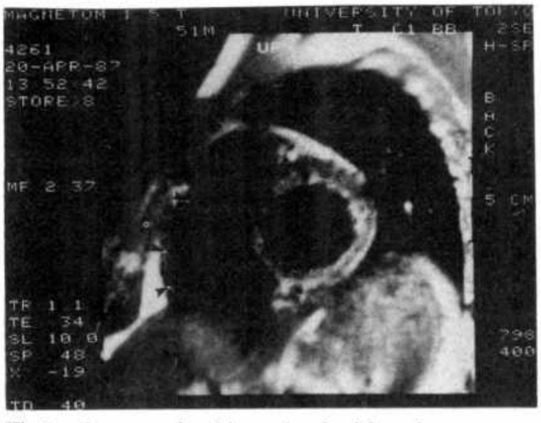

Fig 6 *A cross sectional image in a healthy volunteer. Arrows show the free wall of the right ventricle.*

the t distribution with 18 (19 − 1) degrees of freedom for 0·05 was 2·10. The 95% confidence interval for the bias was −0·06 to −0·02 cm. The confidence intervals for the lower limit of agreement and for the upper limit of agreement were −0·02 to −0·12 cm and 0·04 to 0·12 cm respectively.

RIGHT VENTRICULAR FREE WALL THICKNESS

The mean thickness at 159 points in healthy volunteers, at 303 points in the patients with hypertrophic cardiomyopathy, and at 50 points in the patients with pulmonary hypertension was 0·29 (0·08) cm, 0·44 (0·12) cm, and 0·73 (0·27) cm respectively, and the differences among three groups were statistically significant (p < 0·01) (table 2). The thickest free walls in all patients with hypertrophic cardiomyopathy and in all patients with pulmonary hypertension were 0·7 cm and 1·4 cm respectively. The thickest and the thinnest free wall thicknesses in all healthy volunteers were 0·5 cm and 0·2 cm respectively.

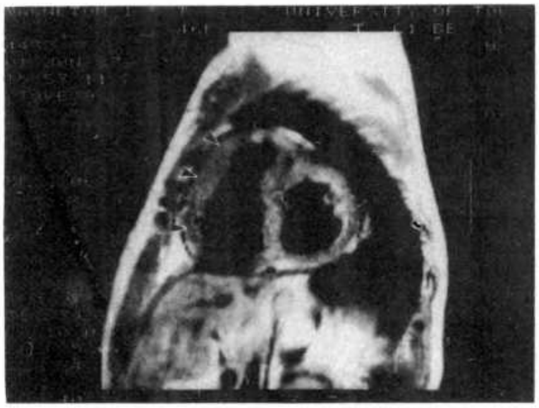

Fig 7 *A cross sectional image in a patient with pulmonary hypertension. Arrows show the free wall of the right ventricle.*

Table 2 *Thickness (mean (1SD)) of the free wall of the right ventricle*

Group	*Mean RVFWT (cm)*	*Maximum RVFWT (cm)*	*Minimum RVFWT (cm)*	*Maximum IVS (cm)*
Normal	0·29 (0·08)	0·42 (0·05)	0·21 (0·03)	1·1 (0·1)
HC	0·44 (0·12)*,**	0·59 (0·10)*	0·31 (0·07)*	2·2 (0·8)*,**
PH	0·73 (0·27)	0·90 (0·35)	0·52 (0·18)	1·0 (0·2)

*p < 0·01 compared with healthy volunteers; **p < 0·01 compared with PH group. IVS, interventricular septum; RVFWT, thickness of the right ventricular free wall.
See footnote to table 1 for other abbreviations.

VARIABILITY IN MEASUREMENTS FROM DIFFERENT VIEWS

In five healthy volunteers we obtained five long axis images that included the right ventricular free wall and we measured the wall thickness at 28 points (table 1). In eight patients with hypertrophic cardiomyopathy we obtained eight long axis images and measured the wall thickness at 37 points. The ratio of the total length of the wall with clear margins to the free wall was 0·62 (65·6 cm/105·2 cm) in this view. The mean thickness of the wall measured on the long axis images was 0·29 (0·08) cm in the five healthy volunteers and 0·46 (0·12) cm in the eight patients with hypertrophic cardiomyopathy. There were no significant differences between thickness measured on the short axis images and that measured on the long axis images.

INTERVENTRICULAR SEPTUM

The maximal thickness of the interventricular septum was 1·1 (0·1) cm in healthy volunteers, 2·2 (0·8) cm in patients with hypertrophic cardiomyopathy, and 1·0 (0·2) cm in patients with pulmonary hypertension.

Discussion

Cross sectional magnetic resonance images clearly distinguished the right ventricular free wall from other surrounding structures in the present study. Adjacent adipose tissue produced the highest signal intensity outside the pericardium, and the pericardium and intrapericardial cavity gave the lowest intensity line.[15] The right intraventricular cavity gave the lowest signal intensity. We had no difficulty in distinguishing these structures from the free wall, which produced a signal band of medium intensity. On average we were able to measure the thickness of 68% of the length of the free wall. We suspect that artefacts caused by chemical shifts or changes in heart rate and arrhythmia during scanning prevented the remainder of the free wall being adequately imaged. Histological examination showed that the normal thickness of the right ventricular free wall was 0·2 cm; a wall thickness of >0·5 cm was regarded as hypertrophic.[7 16]

In echocardiographic studies the free wall was reported to be 0·3 cm thick in healthy volunteers and 0·5 cm thick in patients with hypertrophic cardiomyopathy[9]; however, only a limited number of points were measured. The thickness of the free wall of the right ventricle, which was measured by magnetic resonance imaging at 18 points on average in each patient, was compatible with the results of earlier pathological and echocardiographic studies. Foale *et al* reported that in normal individuals regional variation was quite large for some views.[8] In the present study, the wall thickness in normal volunteers ranged from 0·2 cm to 0·5 cm, and there was little variation between measurements on the short axis and long axis images.

Although we used echocardiographic measurements as a reference standard, it was difficult to obtain images of entire free wall by this method. So echocardiographic measurement was performed at one point in every individual. Magnetic resonance imaging has the advantage of imaging more of the right ventricular free wall (68% in this study) than other methods and this ability is likely to be clinically useful in the diagnosis of several heart diseases. We found that the wall thickness in patients with hypertrophic cardiomyopathy seldom exceeded 0·8 cm but was significantly greater than that of healthy volunteers.

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Transient neonatal tricuspid regurgitation: a Doppler echocardiographic study of three cases

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SUMMARY Three patients with normal hearts and no pulmonary abnormality had neonatal tricuspid regurgitation causing cardiorespiratory distress and cyanosis. The signs of tricuspid regurgitation resolved over a few weeks. In the acute phase echocardiography showed gross dilatation of the right atrium and ventricle. The interatrial septum bulged into the left atrium during the whole cardiac cycle. Doppler echocardiography showed clinically significant tricuspid regurgitation, a right to left shunt through the foramen ovale, reduced flow through the pulmonary valve, and in two patients ductal flow into the pulmonary artery. In one patient tricuspid regurgitation was so great that it impeded the opening of the pulmonary valve and produced functional "atresia" of the pulmonary valve. The presence of regurgitant blood flow through the pulmonary valve showed that the "atresia" was functional rather than organic. Doppler echocardiographic study is useful in distinguishing functional neonatal tricuspid regurgitation from structural abnormality of the tricuspid valve.

The clinical diagnosis of transient neonatal regurgitation is difficult.[1-3] In the past the diagnosis was confirmed by cardiac catheterisation and angiography.[3] It is likely that only patients who were severely affected needed invasive investigation.[4-6] Doppler echocardiography permits an accurate diagnosis of atrioventricular valve regurgitation. Our observations in three infants illustrate the clinical spectrum of transient neonatal tricuspid regurgitation and show the value of Doppler echocardiography in its assessment.

Patients and methods

From August 1985 to the end of February 1986 seven neonates with clinical, radiographic, and echocardiographic evidence of important tricuspid regurgitation and an otherwise structurally normal heart were seen. Three of these patients had severe pulmonary disease: two had hyaline membrane disease and one had pneumonitis caused by meconium aspiration. One neonate presented with congestive heart failure and a hyperkinetic circulation caused by a large cerebral arteriovenous fistula. In the remaining three patients we found no underlying abnormality. In these three patients all signs of tricuspid regurgitation resolved over a few weeks or months. They form the basis of this report.

Doppler echocardiographic studies were performed with commercial units. We did not measure the size of the atrium as there are no universally accepted normal reference standards. Only gross disproportions between the atria were noted. Bulging of the interatrial septum into the left atrium was assessed throughout the cardiac cycle. Dilatation of the right ventricle was measured by comparing the right and left ventricular end diastolic dimensions in the parasternal short axis view. Tricuspid regurgitation was assessed according to the classification proposed by Miyatake *et al.*[7]

The pressure drop across the tricuspid valve during systole was estimated from the maximum flow velocity recorded by continuous wave Doppler and the simplified Bernouilli equation ($p = 4v^2$ where p = peak pressure gradient in mm Hg and v = maximal flow velocity in m/s).

CASE 1

A full term male infant (birth weight 3700 g) was born after an uneventful pregnancy and delivery. The one and five minute Apgar scores were 6 and 8.

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Slight cyanosis, present at birth, persisted with the infant breathing 40% oxygen. A heart murmur was noted at age 8 hours. Because of his increasing tachypnoea and grunting, an endotracheal tube was installed and positive airway pressure ventilation was started. When he was two days old he was transferred to our hospital. There was mild cyanosis and the liver was palpable below the costal margin. Auscultation of the lungs was normal. A grade 4/6 high pitched pansystolic murmur was best heard at the lower left sternal border. The chest *x* ray showed mild cardiomegaly with a cardiothoracic ratio of 0·57 and normal hilar markings. Right atrial enlargement and ST depresssion with negative T waves from V3R to V6 were noted on echocardiography.

Cross sectional echocardiograms showed a structurally normal heart but pronounced dilatation of the right atrium and right ventricle. The interatrial septum bowed towards the left atrium throughout most of the cardiac cycle, suggesting a large pressure difference. A ductus arteriosus was visualised. On M mode echocardiograms the ratio of the right ventricle to the left ventricle at end diastole was 0·86. The next day the condition had improved and the patient could be extubated. Cross sectional echocardiography showed that the right ventricle had become smaller and that there was a straight interatrial septum. Pulsed Doppler showed a grade 3 pansystolic tricuspid regurgitant jet halfway down the right atrium. Because the maximum flow velocity was 3·0 m/s we estimated that the systolic right ventricular-right atrial gradient was 36 mm Hg. All other flow velocities and flow patterns were normal except for turbulence in the pulmonary artery caused by ductal flow. The cardiac murmur disappeared completely over the next week. Follow up examinations at one week and two months were within normal limits.

CASE 2

This male infant was delivered by caesarean section because of fetopelvic disproportion. The mother had been injecting 8 units of insulin daily during the second half of pregnancy. At birth the patient appeared to be normal but a few hours later he became cyanotic and tachypnoeic. Because a heart murmur was heard echocardiography was performed; this led to the tentative diagnosis of "hypoplastic left heart syndrome". When he was two days old he was transferred to our hospital. On examination tachypnoea, mild cyanosis, and gross hepatomegaly were noted. A grade 2/6 systolic murmur and a gallop rhythm were heard at the lower left sternal border. The electrocardiogram was within normal limits. The chest *x* ray showed considerable cardiomegaly (cardiothoracic ratio 0·75) and pulmonary hypoperfusion.

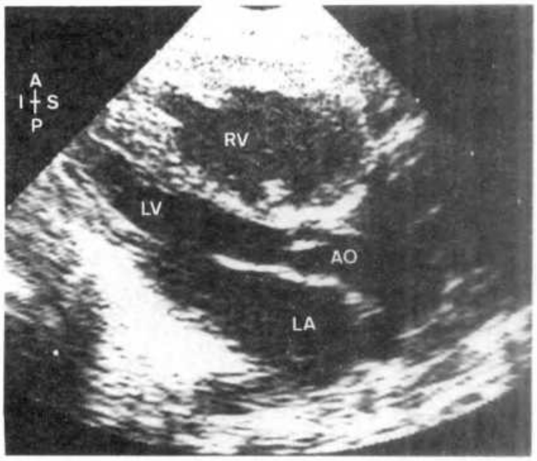

Fig 1 *Parasternal long axis view in patient 2 showing a normal size left heart and a considerably dilated right ventricle. This gross disproportion between the ventricles had led to the erroneous diagnosis of hypoplastic left heart. AO, ascending aorta; LA, left atrium; LV, left ventricle; RV, right ventricle; A, anterior; I, inferior; P, posterior; S, superior.*

Cross sectional echocardiography (fig 1) showed that the dimensions of the left heart were normal but that the right atrium, right ventricle, and pulmonary trunk were grossly dilated. On M mode echocardiograms the ratio of the right ventricle to the left ventricle was 1·0 at end diastole. There was no evidence of a ductus arteriosus. Pulsed Doppler echocardiography showed considerable pansystolic retrograde turbulent flow into the right atrium, corresponding to grade 3 tricuspid regurgitation. A maximum flow velocity of 3·1 m/s indicated a systolic pressure drop of 38 mm Hg from the right ventricle to the right atrium. A small regurgitant jet was recorded just proximal to the pulmonary valve. During the next few days the patient's condition improved rapidly and signs of heart failure disappeared. When he was one week old the systolic murmur and gallop rhythm were no longer audible. On the echocardiogram only borderline enlargement of the right atrium and ventricle persisted. Doppler studies at follow up were within normal limits.

CASE 3

A female infant (birth weight 2900 g) was born after an uncomplicated pregnancy. The mother had taken no medication. The five minute Apgar score was 10. The same day the baby was referred because of suspected congenital heart disease. On physical examination mild cyanosis and tachypnoea were noted. The precordial impulse was active and diffuse. The liver was palpable 4 cm below the costal margin. The second sound was single. A grade 2/6 systolic

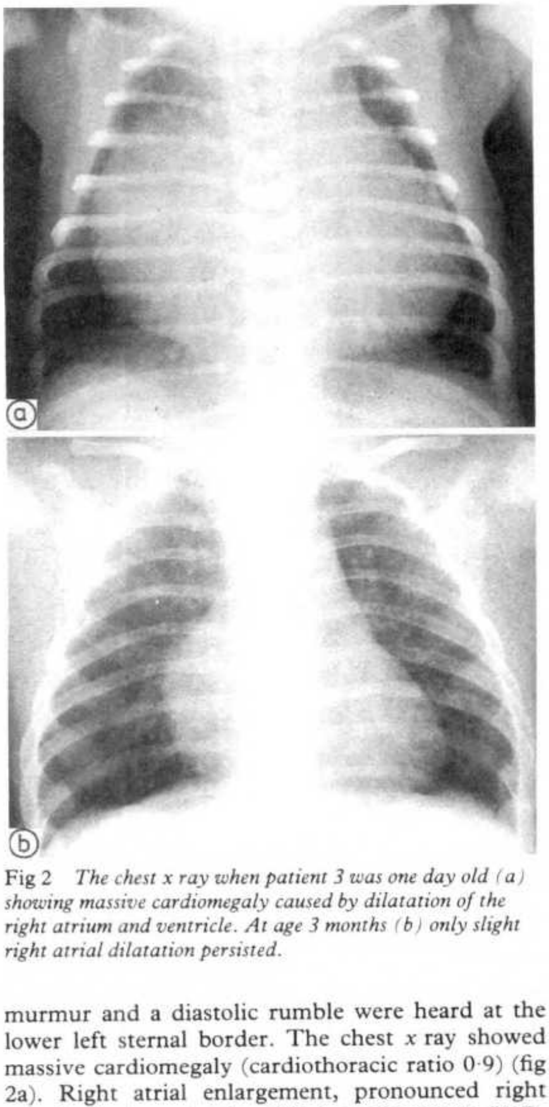

Fig 2 *The chest x ray when patient 3 was one day old (a) showing massive cardiomegaly caused by dilatation of the right atrium and ventricle. At age 3 months (b) only slight right atrial dilatation persisted.*

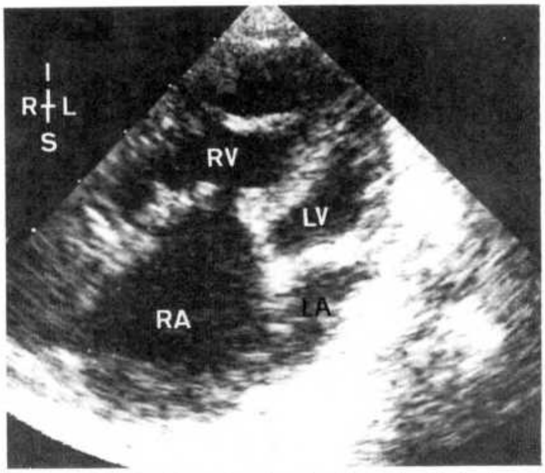

Fig 3 *The apical four chamber view in patient 3 showing considerable dilatation of the right atrium and right ventricle and bulging of the atrial septum into the left atrium. The apex of the heart was found to consist mainly of the right ventricle even when the transducer was moved as far as possible to the left. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; I, inferior; L, left; R, right; S, superior.*

murmur and a diastolic rumble were heard at the lower left sternal border. The chest *x* ray showed massive cardiomegaly (cardiothoracic ratio 0·9) (fig 2a). Right atrial enlargement, pronounced right ventricular hypertrophy with deep Q waves in V3R, and ST changes were noted on the electrocardiogram.

Cross sectional echocardiography showed gross dilatation of the right atrium and right ventricle (fig 3). The interatrial septum bulged into the left atrium throughout the cardiac cycle. The right ventricular outflow tract and pulmonary trunk were well developed. The pulmonary valve was thickened and immobile. The tricuspid valve was echodense but moved well. There was no apical displacement of the annulus. The ductus arteriosus was visualised and retrograde flow was seen in the pulmonary artery. The inferior angle between the ductus and the descending thoracic aorta was obtuse. M mode echocardiograms showed a right ventricular/left ventricular ratio of 1·2. Doppler echocardiography showed no forward flow across the pulmonary valve. A pulmonary regurgitant jet was identified in the right ventricular outflow tract; this finding excluded pulmonary atresia but not severe pulmonary stenosis. The continuous Doppler beam could not be aligned satisfactorily with this regurgitant jet. The maximum recorded speed of 2·9 m/s was consistent with a diastolic gradient across the pulmonary valve of at least 33 mm Hg. A pansystolic tricuspid regurgitant flow was recorded in the entire right atrium and in the hepatic veins. The maximal velocity on a satisfactory signal was 2·9 m/s corresponding to a pressure drop of 33 mm Hg from the right ventricle to the right atrium during systole (fig 4). These findings suggested that pressure in the right ventricle remained below that in the pulmonary trunk throughout the cardiac cycle.

Over a period of three months the clinical condition improved steadily—the respiratory rate became normal and the hepatomegaly and cyanosis disappeared. Physical examination when the patient was five weeks old showed a soft grade 2/6 systolic murmur at the fourth left intercostal space and a normally split second sound. Cross sectional echocardiography showed a striking reduction in the dimensions of the right heart; the right atrium was still slightly dilated but the right ventricle was within

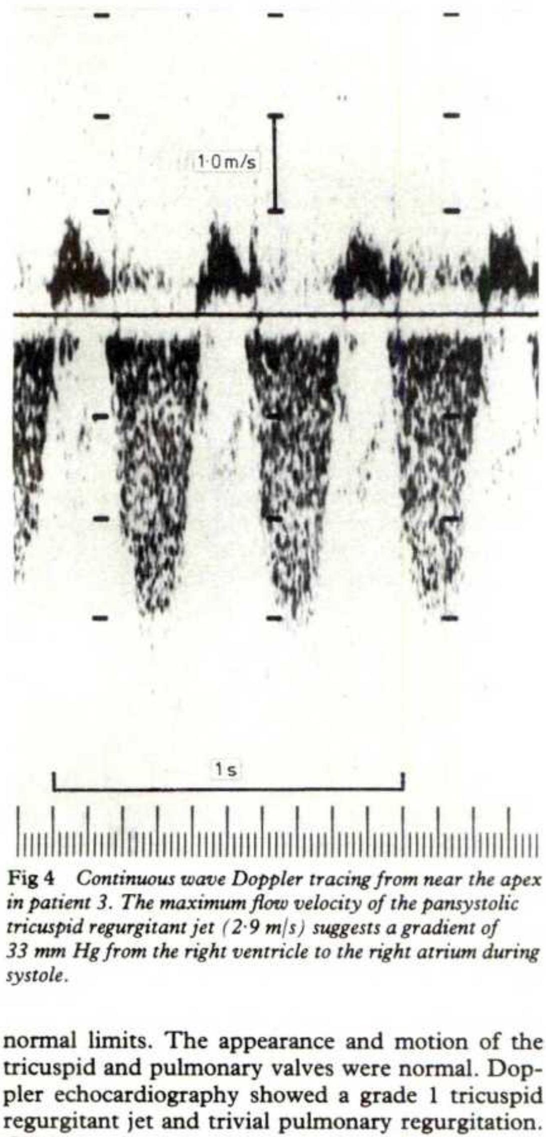

Fig 4 *Continuous wave Doppler tracing from near the apex in patient 3. The maximum flow velocity of the pansystolic tricuspid regurgitant jet (2·9 m/s) suggests a gradient of 33 mm Hg from the right ventricle to the right atrium during systole.*

normal limits. The appearance and motion of the tricuspid and pulmonary valves were normal. Doppler echocardiography showed a grade 1 tricuspid regurgitant jet and trivial pulmonary regurgitation. Clinical, echocardiographic, and Doppler examinations at three and six months were within normal limits. The chest *x* ray showed slight dilatation of the right atrium (fig 2b).

Discussion

Various lesions can cause severe tricuspid regurgitation in the neonatal period. Primary anomalies of the tricuspid valve include Ebstein's malformation, tricuspid valve dysplasia, abnormal attachment of the chordae and papillary muscles, isolated clefts, isolated deficiency of one or more leaflets, unguarded tricuspid orifice, reduplication of the tricuspid orifice, and atrioventricular septal defect.[5,8] Tricuspid regurgitation may also be secondary to severe pulmonary hypertension or obstruction of the right ventricular outflow tract with an intact ventricular septum.[9] Finally, there is a transient form of isolated tricuspid regurgitation that does not have an obvious anatomical and haemodynamic basis.[1-3] It has been suggested that sudden perinatal constriction of the ductus arteriosus forces the right ventricle to pump the entire systemic venous return into the high resistance pulmonary circuit. This might result in right ventricular dilatation and tricuspid regurgitation that would resolve with the reduction of pulmonary resistance and pressure during the first days of life.[2,6,10] Others speculate that perinatal hypoxia leads to myocardial ischaemia and dysfunction of the papillary muscles of the tricuspid valve.[4,11]

The clinical syndrome of transient tricuspid regurgitation in the neonate is variable and depends on the degree of valve dysfunction. In milder forms patients present with slight cyanosis, tachypnoea, and hepatomegaly with a moderately loud systolic murmur at the lower left sternal border. The chest *x* ray shows pronounced cardiomegaly. In these patients the signs of tricuspid incompetence usually resolve within days, as they did in two of our patients (1 and 2). In severe forms (as in patient 3) postnatal distress and congestive heart failure may be life threatening. The electrocardiogram often shows evidence of myocardial ischaemia.[4] Tricuspid regurgitation may be so massive that it impedes opening of the pulmonary valve. Pulmonary blood flow is then completely dependent on the ductus. Considerable shunting of systemic venous blood across the foramen ovale will result in pronounced desaturation of arterial oxygen.[3,5] This conduction is known as "functional pulmonary atresia".[12]

The main difficulty in diagnosis is distinguishing between patients with organic pulmonary atresia, a dilated right ventricle, and tricuspid regurgitation[9] and those with isolated gross tricuspid regurgitation and "functional pulmonary atresia".[5,12,13] The clinical, electrocardiographic, and radiographic findings are similar in these two groups. Cardiac catheterisation may be helpful in excluding pulmonary atresia if the catheter can be advanced into the pulmonary artery. In most cases of severe tricuspid regurgitation, however, this was difficult or impossible.[5,8,12] If right ventricular systolic pressures are higher than systemic values there is a strong likelihood of severe obstruction of the right ventricular outflow and of secondary tricuspid regurgitation. But this anomaly may also be associated with only slightly raised or normal right ventricular pressures.[8] On the other hand, right ventricular pressure in isolated tricuspid regurgitation varied from low[3,6] to considerably raised.[5,8,12] Right ventricular angiocardiography can be equally misleading. In patients with massive tricuspid regurgitation forward flow and passage of contrast material into the pulmonary artery may be minimal or absent, suggesting severe obstruction of the right ventricular outflow tract.[5,8,12] Freedom *et al* emphasised the role of aortography which they found was the only reliable method of distinguishing between functional and structural pulmonary atresia in 33 neonates with various forms of tricuspid regurgitation.[12] In neonates with functional pulmonary atresia aortography showed a normal aortic isthmus (an indication of normal fetal ductal flow), a widely patent ductus arteriosus, a well developed pulmonary trunk, and, without exception, considerable regurgitation of contrast material into the right ventricle.

The clinical distinction between organic and functional pulmonary atresia is of considerable interest because management of the two conditions is different. Exploratory thoracotomy, in an attempt to relieve suspected obstruction of the right ventricular outflow tract, carries a high risk,[5,8] whereas supportive medical treatment, including the administration of oxygen, correction of metabolic abnormalities, and administration of prostaglandins, may rapidly improve haemodynamic function and give time for spontaneous resolution of transient forms of tricuspid regurgitation in the newborn.[3,5,6] We too found that in our patients all signs of tricuspid incompetence resolved within the first days (two patients) or months of life (one patient).

Our study showed that Doppler echocardiography was useful in the evaluation and non-invasive follow up of haemodynamically compromised neonates presenting with tricuspid regurgitation. In all three cases echocardiography showed a structurally normal heart. Gross anomalies of the tricuspid valve, such as Ebstein's disease or severe dysplasia, could be excluded. In the third patient only, the tricuspid valve seemed to be thickened at the first examination, but the insertion of the annulus and the valve motion were normal. We noted changes that were secondary to gross tricuspid regurgitation: both the right atrium and ventricle were considerably dilated and the interatrial septum bowed towards the left atrium throughout the cardiac cycle, suggesting an increase in right atrial pressure. The ratio between the right ventricular and left ventricular end diastolic dimensions measured by M mode echocardiograms was much higher than the normal mean value (0·60 (0·05)) for neonates.[13] The apex of the heart seemed to consist mainly of the right ventricle, even when the transducer was moved as far as possible to the left. In two patients movement of the pulmonary valve was normal or there was premature closure. It looked thickened and immobile in the patient with functional pulmonary atresia. A ductus arteriosus could be visualised in two of the three patients.

Doppler investigation showed moderate to massive tricuspid regurgitation, a right to left shunt through the foramen ovale, normal or reduced flow through the pulmonary valve, and, in the two cases in whom a ductus was visualised, ductal flow into the pulmonary artery. The findings in one patient with massive tricuspid regurgitation and functional pulmonary atresia are of special interest. The characteristic flow pattern of pulmonary regurgitation, which Freedom *et al*[12] showed by aortography, was also displayed by the Doppler signal. Similar Doppler findings were reported in two neonates with functional pulmonary atresia secondary to severe Ebstein's anomaly.[14] Imaging with colour Doppler will probably help to identify pulmonary regurgitation and distinguish between functional pulmonary atresia and organic pulmonary atresia.

Current continuous wave and pulsed Doppler methods are so sensitive that they commonly find regurgitant tricuspid flow patterns in normal individuals.[7,15] Localised retrograde systolic flow, just proximal to the septal leaflets of the tricuspid valve, was detected in more than half of 11 healthy neonates with no clinically apparent tricuspid incompetence examined during the first days of life.[10] In order to distinguish between these trivial forms of regurgitant flow and haemodynamically important tricuspid regurgitation we used several semiquantitative criteria for the area and the duration of retrograde turbulence.[7] In two patients turbulent flow extended halfway into the right atrium and in the remaining patient it was recorded in the entire right atrium and in the hepatic veins. Turbulent flow was pansystolic whereas in normal neonates it was rarely found in more than half of systole.[10] Furthermore, the Doppler findings should be interpreted in conjunction with the echocardiographic signs of tricuspid regurgitation, particularly gross dilatation of the right ventricle and right atrium, which were not seen in normal neonates.[10,13]

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Br Heart J 1988;**60**:452–4

Case reports

Echocardiographic demonstration of *Escherichia coli* endocarditis restricted to the pulmonary valve

NEIL H MURRAY, MARK G CHEESMAN,* MICHAEL MILLAR-CRAIG

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SUMMARY A 25 year old man with no history of heart disease presented with sweats and rigors. Echocardiography showed a large vegetation on the pulmonary valve and blood cultures grew *Escherichia coli*. Because of recurrent pulmonary emboli a large vegetation on the anterior leaflet of the pulmonary valve was excised. He recovered after a full course of antibiotics.

Isolated endocarditis of the pulmonary valve is uncommon and rarely occurs on native valves if there are no predisposing factors such as congenital heart disease or intravenous drug abuse. The pulmonary valve is also the most difficult of the four cardiac

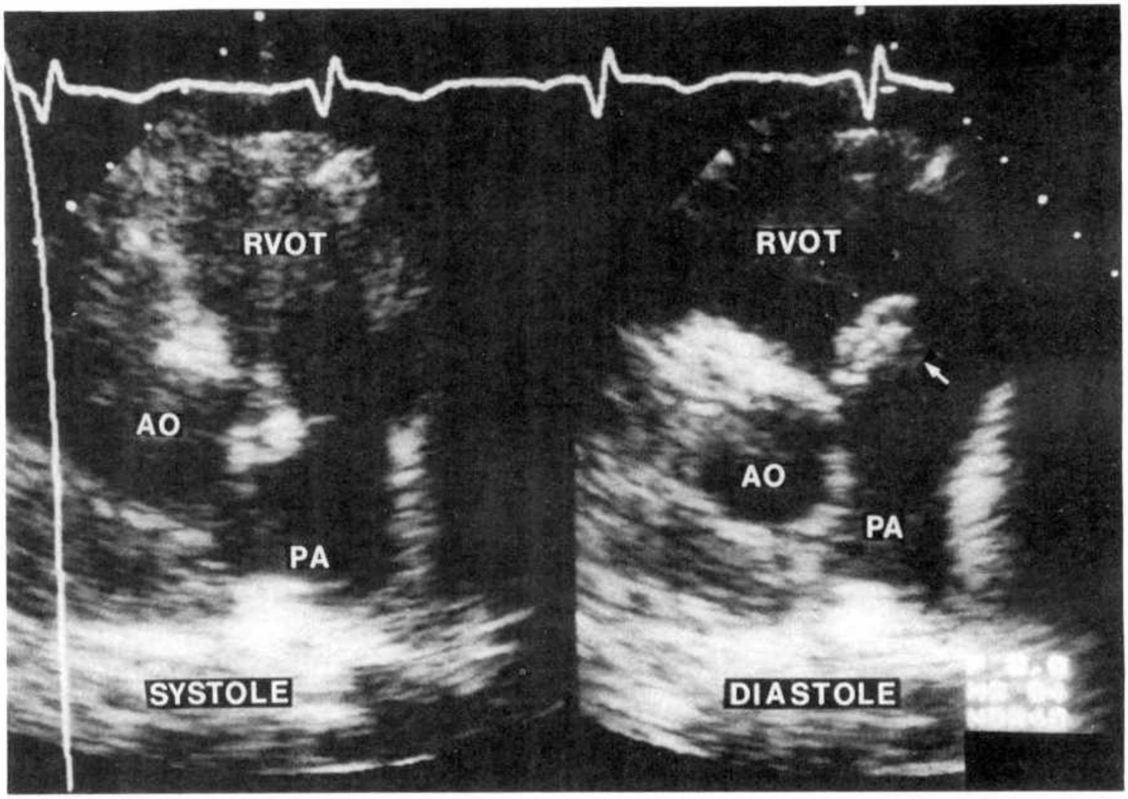

Fig 1 *Parasternal short axis view showing a large vegetation on the pulmonary valve (arrow). RVOT, right ventricular outflow tract; PA, pulmonary artery; AO, aorta.*

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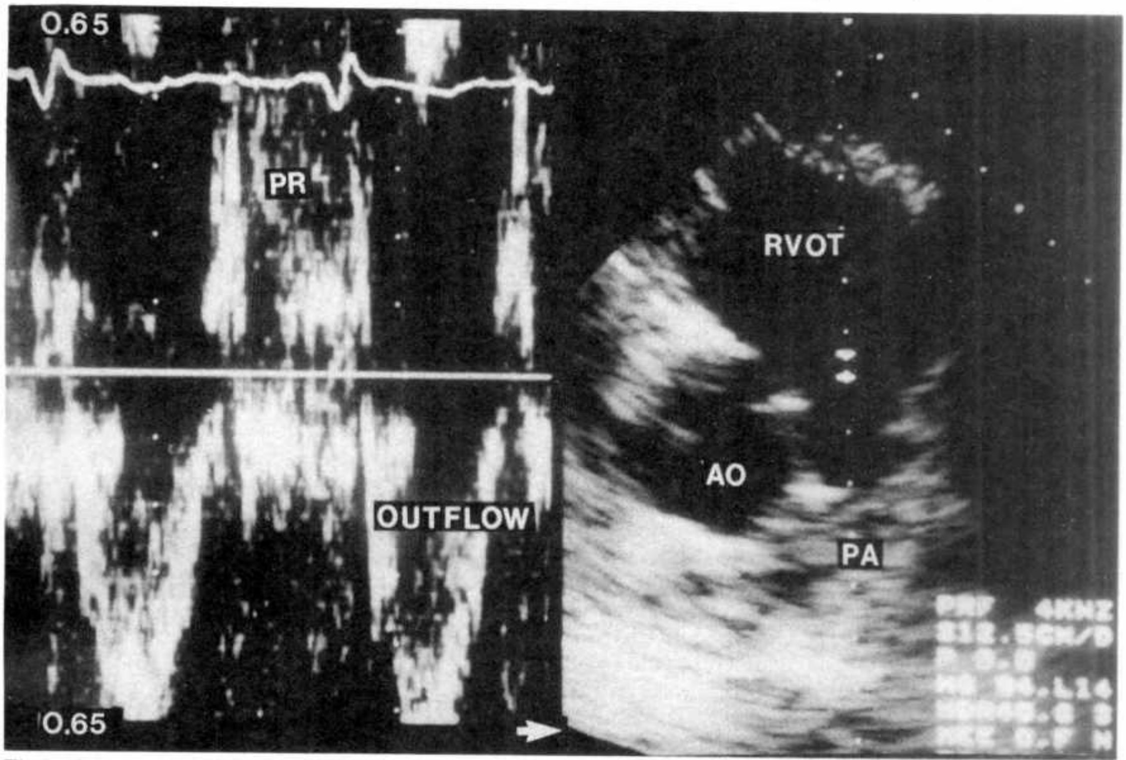

Fig 2 *Parasternal short axis view with pulsed wave Doppler ultrasound showing pulmonary regurgitation (PR). The sample volume is placed at the level of the pulmonary valve. RVOT, right ventricular outflow tract; PA, pulmonary artery; AO, aorta.*

valves to image during echocardiography and there are few reports of vegetations of the pulmonary valve shown by this technique. We present an unusual case of endocarditis of the pulmonary valve that occurred in a patient with a normal heart. A vegetation was detected by cross sectional echocardiography. Because of recurrent pulmonary emboli the vegetation was excised.

Case report

A 25 year old man presented with a one week history of sweats and rigors. There was no history of drug abuse. There were no signs of endocarditis and examination of the cardiovascular system was normal. The resting electrocardiogram and chest radiographs were both normal. The haemoglobin concentration was 145 g/l, the white cell count was $7 \cdot 5 \times 10^9$/l, and the erythrocyte sedimentation rate was 45 mm/hour. Blood cultures grew *Escherichia coli* and Gram negative septicaemia was diagnosed. He was treated with gentamicin, penicillin, and metronidazole. On the fifth hospital day an early diastolic murmur of pulmonary regurgitation was heard and bacterial endocarditis was diagnosed. Despite extensive investigations we found no cause for the underlying infection with *E coli*. Echocardiography at this time was normal. He remained feverish and a second echocardiogram 18 days later showed a thickened pulmonary valve with a 2 cm echogenic mass associated with the valve. This was interpreted as a vegetation (fig 1). Pulmonary regurgitation was detected by Doppler ultrasound (fig 2). Subsequently episodes of pleuritic chest pain with haemoptysis developed and recurrent pulmonary infarction secondary to recurrent septic emboli was diagnosed. He therefore underwent exploration of the pulmonary valve and a large vegetation on the anterior leaflet was resected without valve replacement. His progress after operation was uneventful and his temperature returned to normal with antibiotic treatment. Six months later he was well and had a soft early diastolic murmur of pulmonary regurgitation.

Discussion

Endocarditis restricted to the right heart valves is uncommon.[1] In the absence of congenital heart disease right sided infections are usually caused by a virulent organism or a large inoculation (such as occur during intravenous drug abuse) which usually affect the tricuspid valve rather than the pulmonary valve. The organism that most commonly causes right sided endocarditis is *Staphylococcus aureus*.[1] *Escherichia coli* is rare but has been reported before.[2] None the less, we are not aware of any previous reports of isolated pulmonary valve endocarditis caused by *E coli* that occurred in the absence of the typical predisposing factors. Although virulent organisms are more commonly found in right sided endocarditis the course is less serious than left sided infection.[1] Pneumonia or septic pulmonary emboli, however, are seen in 70–100% of cases of tricuspid endocarditis[3] and Berger *et al* recently described three patients with pulmonary valve endocarditis who presented with pulmonary embolic phenomena.[4] Operation for right sided endocarditis usually involves valve excision with or without implantation of a prosthetic valve.[1] Resection of a vegetation without valve replacement has been performed in a case of tricuspid valve endocarditis,[5] but not to our knowledge on a pulmonary valve. Because our patient was lean he was a suitable subject for echocardiography, but it is often difficult to show the pulmonary valve in adults. Like the patient described by Chambers and Leech,[2] however, pulmonary regurgitation in our patient was easily detected by pulsed wave Doppler ultrasound. This may be a useful marker of pulmonary valve endocarditis in the absence of clear cross sectional echocardiographic images. The signal intensity was much greater than expected with physiological pulmonary regurgitation. We believe that a complete echocardiographic examination for endocarditis should include attempts to image the pulmonary valve and a Doppler ultrasound examination of the right ventricular outflow tract.

We thank Dr J Windebank, Dr P J B Hubner, and Mr R K Firmin for permission to report a patient under their care.

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Intracardiac thrombosis, phospholipid antibodies, and two-chambered right ventricle

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SUMMARY A 34 year old woman with a history of five spontaneous abortions and a systemic lupus-like illness underwent cardiotomy for resection of a calcified right ventricular thrombus. At operation an anomalous right ventricular muscle bundle was discovered under the calcified thrombus. Clinical chemistry showed lupus anticoagulant activity and cardiolipin antibodies in the plasma.

Recently, better characterisation of phospholipid antibodies has led to renewed interest in the "lupus anticoagulant" and its clinical manifestations. We describe a patient who had a systemic lupus-like illness in which the "lupus anticoagulant" and cardiolipin antibodies were associated with intracardiac thrombosis.

Case report

A 34 year old woman with echocardiographic evidence of an intracardiac mass was referred to the Mayo Clinic. Her history included five spontaneous abortions occurring at 16 to 20 weeks of gestation. She had a poorly defined history of pretibial rash, arthralgias, joint swelling, and stiffness which were responsive to corticosteroids. Evaluation at another institution had showed an accelerated erythrocyte sedimentation rate but no antinuclear antibody or rheumatoid factor. There had been no definite additional symptoms, signs, or biochemical or immunological evidence of systemic lupus erythematosus, although she may have had a malar rash in the past. Three years previously, she had had episodic horizontal vertigo without other localising neurological symptoms. Shortly before coming to the Mayo Clinic she underwent echocardiographic evaluation elsewhere to exclude a cardiac source of emboli and for evaluation of a heart murmur. An intracardiac mass was found. There was no family history of systemic lupus erythematosus or lupus anticoagulant activity.

Examination at the Mayo Clinic showed an obese woman with a blood pressure of 142/100 mm Hg and a regular heart rate of 85 beats/min. The lungs were clear. Her jugular venous pressure was not elevated, but she had prominent "a" and "v" waves in her neck. Her carotid arteries had a normal upstroke but decreased volume. Her precordium was unremarkable. Auscultation revealed a normal S_1, a single S_2, a loud S_4, an early systolic sound, and a grade 3/6 ejection murmur heard prominently at the base to the left of the sternum. The Valsalva manoeuvre and handgrip test reduced the intensity of the murmur.

The concentration of haemoglobin was increased (155 g/l). Serum concentrations of cholesterol and triglyceride were normal. Serum protein electrophoresis showed a raised γ globulin fraction (22·4 g/l). There were no monoclonal proteins in the urine or serum. The assay for antinuclear antibody was positive (1:640) and showed a mixed pattern. Total haemolytic complement was 15 units (normal, 25–70), C3 was 670 mg/l (normal, 880–2050), and C4 was 110 mg/l (normal, 1150–2680). The erythrocyte sedimentation rate was 24 mm in one hour. The test for rheumatoid factor was negative. She had a positive serological test (rapid plasma reagin) (1:4), but a negative specific test for syphilis (fluorescent treponemal antibody absorption). There were no antibodies to extractable nuclear antigens. There were IgG cardiolipin antibodies (1:16) but not IgM cardiolipin antibodies.[1]

Coagulation studies showed normal bleeding time (Ivy) and normal platelet count (170 000/mm^3). The prothrombin time was slightly prolonged and inhibited (23 seconds; normal 17–19). The plasma recalcification time with platelet rich plasma was

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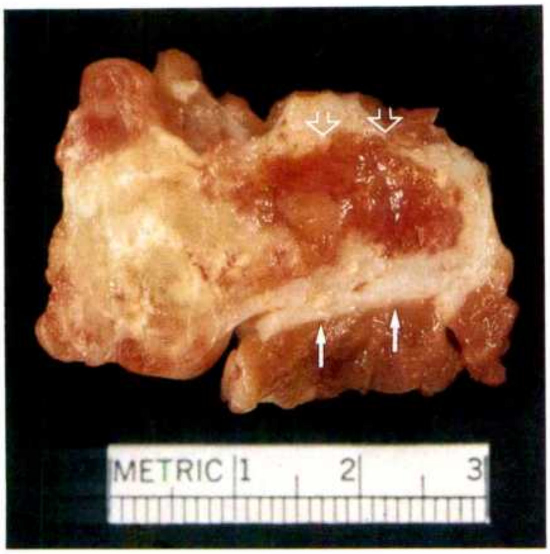

Fig 1 *Specimen from right ventricle showing site of resected muscular diaphragm (below solid arrows), endocardial fibrosis and calcification (solid arrows), and thrombus (open arrows).*

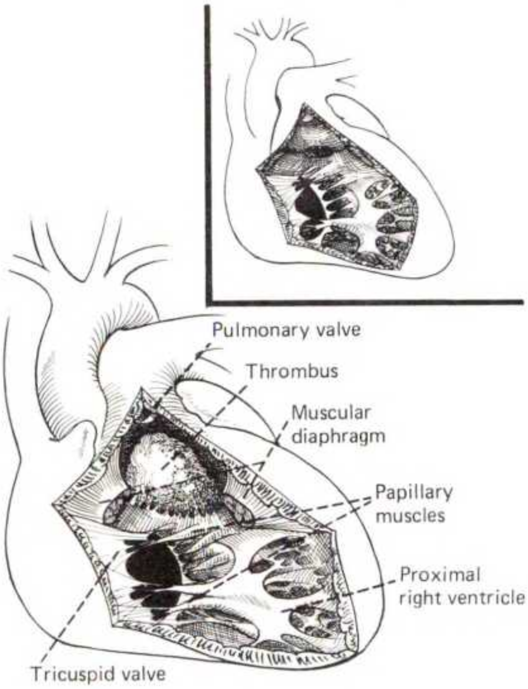

Fig 2 *Drawing of operative view of right ventricular thrombus and anomalous muscle bundles. Inset, after resection.*

prolonged and inhibited in mixing tests with normal plasma (plasma clot time 149 seconds; normal 70–90). The activated partial thromboplastin time was 95 seconds (normal 25–40) and was also inhibited in mixing tests. Specific clotting factors were not inhibited, and there was significant correction of the prolonged activated partial thromboplastin time in the platelet neutralisation procedure—a positive test. These findings are diagnostic of the lupus-like anticoagulant.

An electrocardiogram showed normal sinus rhythm and a P wave with a vertical axis. An *x* ray of the chest showed a prominent right atrium and right ventricle. A cross sectional echocardiogram showed dilatation of the right atrium and right ventricle and a calcified right ventricular mass attached near the papillary muscles of the tricuspid valve that extended into the right ventricular outflow tract. Doppler examination showed tricuspid insufficiency. Magnetic resonance imaging showed a 1·5 × 2·5 × 6·0 cm mass. Because of concern about the risk of thromboembolism, cardiac catheterisation was not performed.

The patient's constellation of symptoms, physical findings, and laboratory data resembled that of systemic lupus-like illness but did not satisfy the American Rheumatological Association's criteria for the classification of definite systemic lupus erythematosus.[2]

An operation was recommended. At right ventriculotomy, inspection showed multiple muscle bundles dividing the inflow portion of the right ventricle from the outflow portion (as with a two-chambered right ventricle). A large mass that was attached to this muscular diaphragm and protruded into the subpulmonary valve region was excised from the surrounding scar tissue (figs 1 and 2). The tricuspid valve apparatus was not affected. Histology showed partial organisation of necrotic thrombus, endocardial fibrosis, and focal fibroblastic proliferation; focal areas of fine calcific deposits; and focal clusters of chronic inflammatory cells (primarily lymphocytic, with focal accumulations of many eosinophils and plasma cells). Typical Libman-Sachs vegetation was not seen.

The patient had an uneventful recovery after the operation. At discharge she was advised to continue warfarin treatment indefinitely, and she was considering a sterilisation operation.

Discussion

Systemic lupus erythematosus has long been recognised as being associated with in vitro anticoagulant activity.[3] In 1963, Bowie and colleagues described four of eight patients who had lupus anticoagulant activity associated with thrombosis.[4] The term "lupus anticoagulant" was coined by Feinstein and Rapaport in 1972,[5] and much interest has been generated recently by the clinical expression of this syndrome.[6-12] The understanding of thrombosis associated with lupus anticoagulant activity has been further defined by the recognition of the role of cardiolipin antibodies in these phenomena.[13-18]

Cardiac manifestations of systemic lupus erythematosus and lupus-like illnesses are common. In 1924, Libman and Sacks reported valvar and mural endocarditis associated with systemic lupus erythematosus.[19] Since their initial report, systemic lupus erythematosus has been shown to have protean cardiovascular manifestations.[20 21] These have included pancarditis with pericardial thickening and effusion, coronary artery disease with myocardial infarction, and, rarely, coronary arteritis. Reported valvar lesions have included Libman-Sacks endocarditis, valvar thickening, aortic insufficiency, mitral regurgitation, and infective endocarditis. Echocardiographic findings have included pericardial thickening, thickened aortic and mitral valves, and calcification of the mitral annulus.[22] To our knowledge, an intracardiac mass in a patient with a lupus-like illness, lupus anticoagulant activity, and cardiolipin antibodies has not been reported before.

We did not find pericardial involvement or histological evidence of Libman-Sacks endocarditis in our patient. We saw no valve thickening at ventriculotomy. The normal peripheral eosinophil count and the appearance of the endocardium at operation excluded the hypereosinophilic syndrome.

Special coagulation features and clinical biochemical correlates of lupus anticoagulant activity and phospholipid antibodies were found in our patient, including prolonged phospholipid-dependent coagulation, inability to restore normal prothrombin time and activated partial thromboplastin time during mixing studies, a positive platelet neutralisation test, and raised titres to cardiolipin antibodies.

We speculate that an abnormal flow pattern in the right ventricle (caused by the anomalous muscle bundles), associated with a tendency to thrombosis because of the cardiolipin antibodies, led to the formation of the intracardiac mass in our patient.

Six months after operation the patient was symptom free. Although there are no data on the efficacy of long term anticoagulation in preventing recurrent thrombosis in this setting, the reports by Hughes[16] and Gastineau *et al*[6] suggest that oral anticoagulation may be protective. In addition, Asherson *et al* have reported that warfarin withdrawal is associated with a high incidence of recurrent thrombosis.[17] So we plan to treat the patient with warfarin anticoagulation indefinitely.

We thank Dr Henry A Homburger, for performing the assays for cardiolipin antibodies and Dr Harvinder S Luthra and Dr Francis J Kazmier for their advice on the paper.

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Notices

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 22 to 24 November 1988. The closing date for receipt of abstracts was 24 June 1988.

The Annual General Meeting for 1989 will take place in Oxford on 6 and 7 April 1989, and the closing date for receipt of abstracts will be 6 January 1989.

Preventive cardiology

The 2nd International Conference on Preventive Cardiology (sponsored by the Council on Epidemiology, American Heart Association) will take place in Washington, DC, on 18 to 22 June 1989. For details write to Secretariat, 9650 Rockville Pike, Bethesda, Maryland 20814, USA.

Atrial arrhythmias

An international symposium on Current Concepts in the Study and Management of Atrial Arrhythmias will be held in Lyon on 6 to 8 December 1989. For further information write to Professor P Touboul, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, BP Lyon Montchat, 69394 Lyon Cedex 3, France.

Electrocardiography

A meeting on Electrocardiography: Past and Future will be held in Nice on 7 to 9 September 1989. For further information contact the Conference Department, The New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021, USA.

Diseases of the chest

The 16th World Congress on Diseases of the Chest will be held at the Sheraton-Boston Hotel and Towers and the John B Hynes Convention Auditorium on 30 October to 3 November 1989. Information from Division of Education, American College of Chest Physicians, 911 Busse Highway, Park Ridge, IL 60068-2375, USA.

British Nuclear Cardiology Group

The annual meeting of the British Nuclear Cardiology Group will be held at the Robin Brook Centre, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE on 21 November 1988. For further details contact Dr Richard Underwood, MR Unit, National Heart and Chest Hospitals, 30 Britten Street, London SW3 6NN (01-351 5773).

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Morphology of the endothelium over atherosclerotic plaques in human coronary arteries

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SUMMARY The right coronary arteries of six hearts removed from patients with atherosclerosis, who were undergoing cardiac transplantation, were perfused with 2% buffered glutaraldehyde for 20 minutes before preparation for scanning electron microscopy. Perfusion was started within five minutes of explantation. In two patients the artery was angiographically normal, in one it was irregular in outline, and three had focal segments with significant stenosis. None of the patients had concentrations of plasma lipids above 5·5 mmol/l. The endothelial surface showed widespread focal abnormalities ranging from adhesion and migration of monocytes to loss of individual endothelial cells. Larger areas of endothelial denudation with exposure of underlying collagen were also seen consistently. Loss of endothelial cells was associated with accumulation of monocytes, on and deep to the surface, as well as adhesion of platelets to the exposed subendothelial tissue.

These results accord with the endothelial damage and platelet adhesion seen in hyperlipidaemic animals fed a high lipid diet.

Lesions resembling those seen in human atherosclerosis were induced by diets rich in fat that caused hyperlipidaemia in a wide range of animals including pigs,[1] rodents,[2] rabbits,[3] and primates.[4-6] Hyperlipidaemia caused by inherited abnormalities of lipid metabolism in the rabbit also led to the development of atherosclerosis.[7 8] These animal models permitted the sequence of changes in the vessel wall to be followed serially, and they consistently showed that the first morphological change in the development of atherosclerosis was adhesion of monocytes to an intact endothelial surface followed by their migration into the intima,[2] a process that begins within 12 days of the start of a high lipid diet in primates.[4] By 12 weeks sufficient foam cells appeared within the intima to form fatty streaks and most of these lipid filled cells were believed to be macrophages.[3 9 10]

Demonstrable morphological changes were preceded by an increased rate of replication of endothelial cells[11] associated with enhanced permeability to Evans Blue and it was at such sites that monocyte adhesion occurred.[12] It has been suggested that the early increase in the turnover of endothelial cells is associated with increased desquamation of endothelial cells[13] but not with exposure of the subendothelial collagen. The mechanism by which monocytes react with intact endothelial cells is unclear. On one hand, hyperlipidaemia may produce functional changes in the endothelial and smooth muscle cells—for example, increasing the expression of factors that are chemotactic for monocytes.[14] On the other hand, hyperlipidaema or hyperfibrinogenaemia may enhance the capacity of circulating monocytes to adhere to endothelial surfaces.[15-17]

The appearance of fibro-lipid plaques in animal models of atherosclerosis was associated with a considerable increase in the adhesion of monocytes to the endothelial surface and morphological evidence suggesting that lipid filled macrophages were both entering and leaving the intima.[5 18] At this stage, usually 3–4 months after the onset of hyperlipidaemia, smooth muscle migration into the intima was also well established. The presence of large aggregates of lipid filled macrophages then became associated with focal defects in the endothelial lining that exposed collagen, and in some models platelet adhesion was seen in such areas.[5 19]

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Animal models have therefore given considerable insights into the injury of the arterial wall caused by hyperlipidaemia. All animal models, however, have limitations[20] and we cannot be certain that the sequence of cellular change is the same in humans who are not clinically hyperlipidaemic but who have atherosclerosis.

It is difficult to obtain suitable material in which to examine the endothelium over human atherosclerotic plaques. After death deposition of a superficial layer of polymerised fibrin on the inner surface of the vessel makes it impossible to see the underlying endothelium clearly by scanning electron microscopy. Endarterectomy specimens are a source of atherosclerotic plaques from living patients but damage during sugical removal leads to considerable artefactual change in the endothelium. Many of the difficulties in assessing the integrity of the endothelium over atherosclerotic lesions in human beings can be overcome by examination of explanted hearts removed during cardiac transplantation. We report the results of a preliminary study of six such hearts.

Patients and methods

Hearts were obtained from six patients undergoing cardiac transplantation. All six had varying degrees of coronary atherosclerosis. Five were male and one was female, and all were less than sixty. Plasma total cholesterol concentrations ranged from 2·0 to 5·5 mmol/l; plasma triglyceride concentrations were not raised. In two of the patients the right coronary artery was angiographically normal; in one it had an irregular outline, and in three there were segments showing severe stenosis. In all cases the hearts were removed at operation after cross clamping the aorta; intracoronary perfusion of the recipient heart was not started during the operation. The patients were anticoagulated with heparin as part of the surgical procedure. The orifice of the right coronary artery was cannulated less than five minutes after removal of the heart from the patient and the artery was perfused with 2% buffered glutaraldehyde at a pressure of 130 mm Hg at 4°C for 20 minutes. Because fresh tissue was needed for other studies a similar technique was not used on the left coronary artery. The right coronary artery, from its origin to the origin of the posterior descending coronary artery, was dissected free from the underlying heart and stored in buffered glutaraldehyde. The coronary artery was then divided into segments that were 1–1·5 cm long. Small portions of vessel wall (0·2 cm long) were removed from the ends of each segment and processed for routine microscopy. The remaining part of each segment was processed routinely for scanning electron microscopy and critically point dried before being carefully bisected longitudinally and coated with gold-palladium. The coated samples were examined in an ISI DS130 scanning electron microscope, operating at a voltage of between 10 and 20 kV.

Results

Where examination of the intima at low magnifications showed no atherosclerotic lesions the endothelial surface was intact and the cells were aligned with their long axes in the direction of blood flow (fig 1). Endothelial cells over atherosclerotic lesions of all types, however, were irregularly arranged and varied in size and shape (fig 2). Simple fatty streaks had an intact endothelial covering (fig 3).

In all cases leucocytes adhered to the plasma membrane of the endothelial cells in many areas, both over diffuse intimal thickening and localised plaques (fig 4). The surface of the underlying endothelial cell beneath adherent cells was often indented

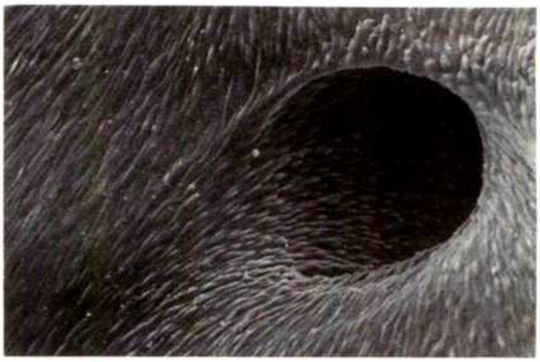

Fig 1 *Normal intact endothelium at a point of arterial branching. The long axes of the cells are aligned in the direction of flow (original magnification, × 278).*

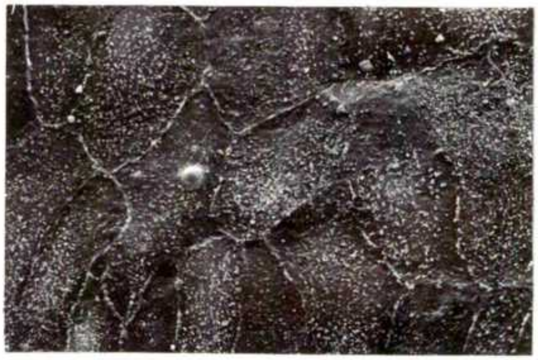

Fig 2 *Intact endothelium over plaque surface showing variation in shape and size of cells and loss of normal orientation. The plasma membranes of the cells have short stubby surface processes (original magnification, × 1480).*

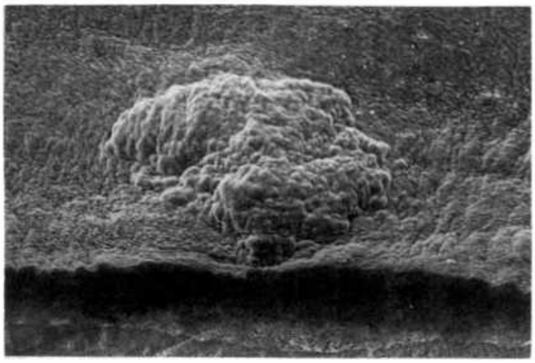

Fig 3 *Micrograph showing a small and complete fatty streak. There is no defect in endothelial integrity but the cells are strikingly raised above the surface of the normal surrounding endothelium because of the subendothelial accumulation of foam cells (original magnification, × 106).*

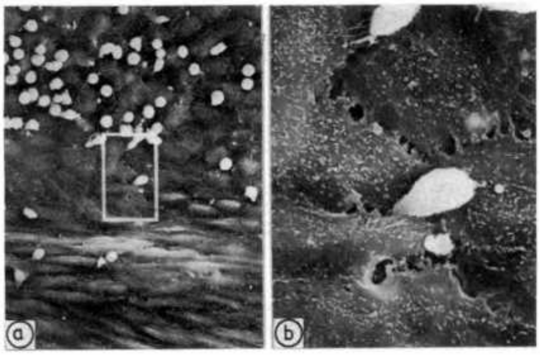

Fig 4(a)/(b) *Leucocytes adherent to an intact endothelial surface over an atherosclerotic plaque. An adjacent area with endothelial cells showing more normal alignment is not associated with leucocyte adhesion (original magnification,* × 407). *The higher magnification shows a leucocyte, probably monocytic, in transit between the endothelial cells (original magnification, × 2035).*

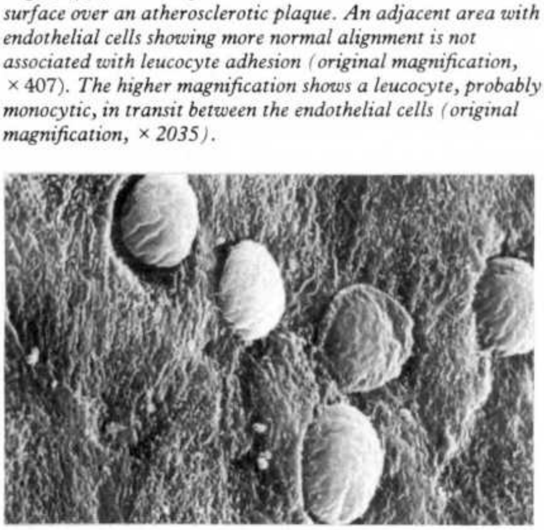

Fig 5 *Leucocyte adherence to intact endothelial cells. The adherent cells appear to settle within small indentation in the plasma mambrane (original magnification, × 2200).*

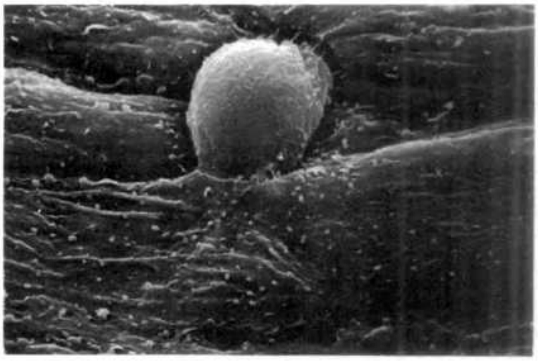

Fig 6 *Leucocyte, part of which is inserted under the edge of an intact endothelial cell (original magnification, × 3870).*

(fig 5). Leucocytes seemed to be in transit through the endothelium (fig 6); some were strikingly elongated at one pole and attached to the subendothelium via a small but distinct gap in the endothelium (fig 7a and b). Many of the migrating leucocytes had a ruffled plasma membrane suggesting a monocytic origin. Where gaps in the endothelium were larger cells with similar morphological appearances could be seen in the most superficial portions of the intima just beneath the endothelial surface (figs 8 and 9).

In all six hearts there were defects in the endothelial surface over plaques; and the more severe the extent of intimal disease in any individual patient the more severe and extensive was this change. But endothelial damage was not, however, directly related to the presence or absence of stenosis; it was often found in segments of artery in which there was no significant obstruction. Exposure of subendothelial collagenous tissue took various forms. In some areas loss of a single endothelial cell caused a clearly demarcated defect in the surface; such defects were associated with the presence of adherent platelets (fig 10). Larger gaps in the endothelial surface were seen where groups of endothelial cells had been lost (fig 11). Endothelial denudation was often but not always associated with the presence of platelets (fig 12).

Discussion

All of the patients in this study were undergoing cardiac transplantation because they had advanced atherosclerosis. Morphological damage to the endothelium was common and widespread. Such a study cannot give information on the possible role of endothelial dysfunction in the early stages of atheroma, but it showed that in common with many animal models endothelial denudation in man is a late phenomenon. In this context "late" refers to the

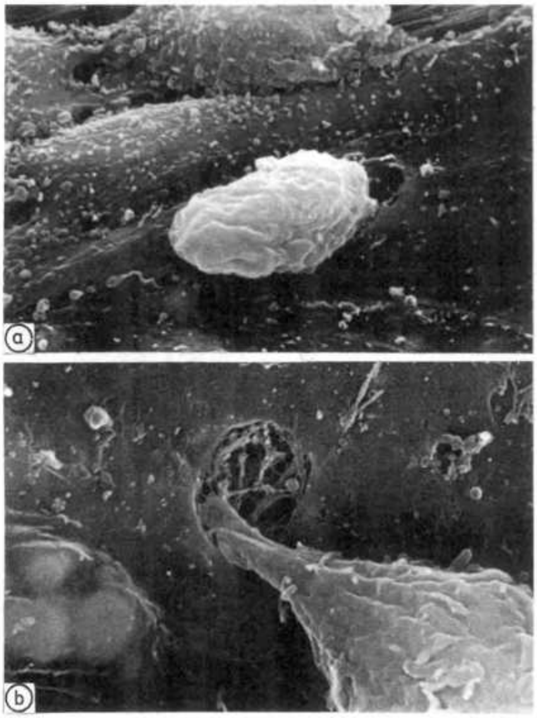

Fig 7 *Leucocyte migration. In (a) the cell is closely applied to a small defect in the endothelial surface (original magnification, × 4430). In (b) the cell is attached to a defect in the endothelium by a strand of cytoplasm. An adjacent area of intact endothelium shows a lipid containing cell immediately beneath the surface (original magnification, × 9800).*

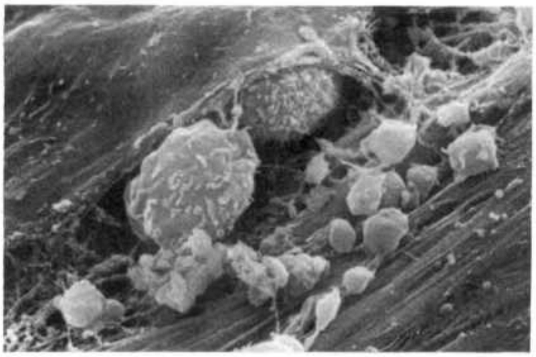

Fig 8 *Fenestrations in the endothelial surface covering two macrophages which are immediately beneath the surface. There are platelets adhering to the exposed subendothelial tissue (original magnification, × 5300).*

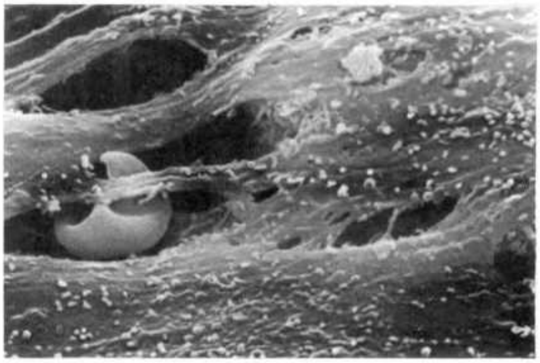

Fig 9 *Endothelium in which there is a defect in the surface that exposes the underlying connective tissue, but no platelet adherence has occurred. A red cell is trapped under a strand of endothelial cytoplasm (original magnification, × 2690).*

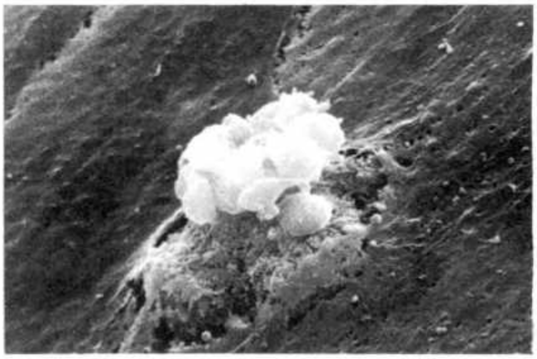

Fig 10 *Loss of a single endothelial cell. The exposed surface is covered by platelets some of which have changed shape (original magnification, × 3570).*

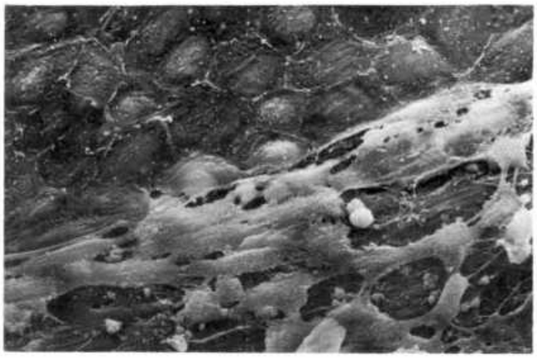

Fig 11 *Large area of endothelial damage with exposure of the underlying connective tissue but minimal platelet adherence. An immediately adjacent area of endothelium is intact but of irregular pattern (original magnification, × 880).*

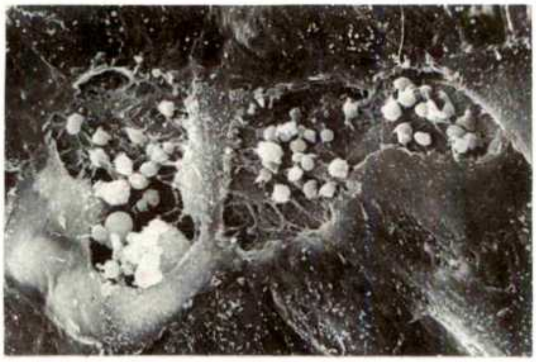

Fig 12 *Endothelial damage and denudation with platelets adhering to the exposed subendothelial tissue (original magnification, × 1340).*

overall degree of intimal involvement and not the degree of stenosis caused by a particular plaque. Endothelial damage was present in many segments without significant obstruction, which shows that angiography is an insensitive method for the detection of diffuse non-stenosing intimal disease.

All the morphological changes noted in this study of human atherosclerosis have been seen in the lesions that develop as a consequence of hyperlipidaemia, whether diet related or inherited, in animal models. Our study showed that monocyte/endothelium/platelet reactions were also present in human atherosclerotic lesions and gave clear evidence of both monocytic adhesion to an intact endothelial surface and focal endothelial denudation over more advanced plaques in the coronary arteries of patients who were not grossly hyperlipidaemic. We do not believe that the endothelial defects can be the result of artefact because many of them were covered by a layer of platelets, most of which had changed shape. Such a process is unlikely to have occurred during the preparation of the tissue samples. If the endothelial changes were purely secondary to the stress of awaiting cardiac surgery, with the inevitable increase in endogenous catecholamine release, we would not have expected to see a selective effect on the atheromatous lesion. All of the patients had morphologically intact endothelium in other areas.

A morphological study cannot establish the direction of migration of individual monocytes. Over early lesions, however, we saw portions of monocyte cytoplasm within the junctions between intact endothelial cells, which suggests that the monocytes were entering the intima. In more advanced atheromatous lesions macrophages were associated with larger defects in the endothelial surface. In these areas endothelial cells were stretched over underlying cells that bulged toward the lumen. Such major defects in the endothelium may well allow lipid filled monocytes to be released into the lumen. All the morphological changes seen in animals and taken to indicate emigration of lipid filled cells from the intima[18] were also seen in our study of human material. The association of denuding endothelial damage with macrophages lying immediately beneath the surface also accords with a direct cytotoxic effect on the endothelium. Morphological studies cannot, however, elucidate the mechanism of such an effect; one of many possibilities is the generation of reactive oxygen species.[19]

The finding of endothelial denudation and platelet interaction with the vessel wall in animal models has given rise to the hypothesis that growth factors derived from platelets cause smooth muscle proliferation and plaque growth.[21] The observed abnormal vasomotor responses of atheromatous arteries in both animal models and man[22-24] have also been explained by endothelial damage and platelet deposition.[25 26] The present study of human endothelium over atheromatous plaques indicates that these hypotheses are tenable in man.

The results reported here are preliminary. The degree of endothelial damage needs to be measured with regard to individual factors such as smoking and blood lipid levels as well as local factors such as the degree of stenosis and arterial geometry.

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Smoking and acute coronary heart disease: a comparative study

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SUMMARY Nine hundred and seventy eight patients with a first documented myocardial infarction were studied to detect smoking related differences in clinical profile and in-hospital outcome. The distribution of infarct sites differed significantly between smokers and non-smokers. Smokers had higher peak cardiac enzyme concentrations. In spite of this, smokers had a better prognosis than non-smokers.

There are important differences between smokers and non-smokers, both in clinical profile and in-hospital outcome, which may reflect a difference in the nature of the underlying coronary disease.

Smoking is a major risk factor for coronary heart disease. Although the long term prognosis after a first myocardial infarction has been compared in smokers, non-smokers, and ex-smokers,[1] the relation of smoking status to the manifestations of acute coronary heart disease remains unclear.

The purpose of this study was to examine the extent to which smokers, non-smokers, and ex-smokers show discernible differences in clinical profile and in-hospital outcome after a first myocardial infarction.

Patients and methods

From January 1980 to April 1985 inclusive, all patients admitted to the coronary care unit of St Vincent's Hospital with a first episode of unstable angina or myocardial infarction were included in a computerised register.

Myocardial infarction was diagnosed when there was typical cardiac pain at rest with abnormal Q waves in the electrocardiogram or a twofold or greater rise in serial cardiac enzymes (serum glutamic oxaloacetic acid transaminase, creatine kinase, and lactate dehydrogenase) or both. Unstable angina was diagnosed on the basis of cardiac pain at rest with serial ST and T wave changes in the electrocardiogram but with normal or a less than twofold increase in the activity of cardiac enzymes.

The site of infarction was classified as anteroseptal, when the electrocardiographic changes were in leads V1–V4; anterolateral with changes in leads V3–V6; and inferior with changes in II, III, and a Vf, with or without changes in V4–V6. Patients with changes in V1–V6 were classified as having combined anteroseptal/anterolateral infarctions. Too few patients had infarction at other sites, a site that could not be determined, and left bundle branch block (which precludes identification of infarct site) for statistical comparisons of such groups to be made. These patients were omitted from analyses of infarct site. Non Q wave infarction was diagnosed when there was cardiac pain, a greater than twofold increase in the activity of cardiac enzymes, and no fresh Q waves in the electrocardiogram.

The presence of angina of effort before infarction was recorded, as were smoking habits before infarction. Preinfarction angina was classified as chronic if it had been present for at least three months before admission, and recent if it had appeared less than three months but more than one week before admission. Patients were classified as non-smokers if they had never smoked as many as one cigarette per day regularly, ex-smokers if they had smoked less than one cigarette per day for at least three months before admission, and current smokers if they had regularly smoked at least one cigarette per day in the three months before admission. Pipe and cigar smoking were noted. Current and former pipe or cigar smokers were classified as current or ex-smokers in the same way as cigarette smokers. To be classified as an

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Table 1 *Admission characteristics (number (%)) of the study group*

	Smoking status				
	Never smoked	*Ex-smoker*	*Current smoker*	*Total*	*p*
Sex:					
Male	81 (40·9)	196 (74·2)	362 (70·3)	639 (65·4)	
Female	117 (59·1)	68 (25·8)	153 (29·7)	338 (34·6)	<0·001
Mean age (SD)	65·6 (10·5)	62·8 (10·6)	57·6 (10·7)	60·6 (11·2)	<0·001
Cholesterol (SD):					
Total (mg/dl)	252 (59·5)	236 (50·8)	241 (56·5)	242 (55·9)	=0·040
HDL fraction (mg/dl)	44·1 (14·4)	39·6 (14·6)	40·1 (15·4)	40·6 (15·0)	=0·022
Hypertension present	101 (51·5)	93 (36·2)	124 (24·7)	318 (33·3)	<0·001
Diabetes mellitus	17 (9·2)	20 (8·1)	32 (6·5)	69 (7·4)	NS
Total	198 (20·3)	264 (27·0)	515 (52·7)	977 (100)	

Missing data: age, 7 cases; cholesterol, 202; HDL, 411; hypertension, 22; diabetes, 49.
Significance levels based on χ^2 (categorical) and Kruskal-Wallis one way analysis of variance (metric variables). HDL, high density lipoprotein cholesterol.

ex-smoker they had to have stopped for at least three months.

Concentrations of total serum cholesterol and the high density lipoprotein fraction were assayed in blood samples taken in most cases within 12 hours of onset of acute symptoms.

In-hospital mortality and complications were recorded. Complications were categorised by a standard protocol that included a total of 31 individual complications. In this paper we will report on four groups of complications:

Mechanical complications.—left ventricular failure, cardiogenic shock, hypotension.

Ventricular arrhythmias.—ventricular fibrillation, ventricular tachycardia, asystole.

Supraventricular arrhythmias.

Atrioventricular blocks (first, second, and third degree).

Patients were categorised as hypertensive if (*a*) the mean of all diastolic blood pressure measurements taken on the fourth day after admission was ≥90 mm Hg; or (*b*) the patient was known to have been treated for hypertension before admission; or (*c*) at least two of the following three were present: past history of hypertension, electrocardiographic evidence of left ventricular hypertrophy, hypertensive retinopathy.

Peak activities of cardiac enzymes were noted as was the presence of diabetes mellitus.

Categorical variables were analysed by the χ^2 test and metric variables by the Wilcoxon rank sum test or Kruskall-Wallis one way analysis of variance by ranks. The latter tests were chosen because some of the metric variables were not normally distributed.

Results

Nine hundred and seventy seven patients were admitted to the study. A further ten patients who fulfilled the entry criteria and were admitted during the study period were excluded from the study because we could not record their smoking habits.

Table 1 shows the admission characteristics of the group. There were 198 (20·3%) patients who had

Table 2 *Smoking and manifestations of acute coronary heart disease (number (%))*

	Smoking status				
	Never smoked	*Ex-smoker*	*Current smoker*	*Total*	*p*
Previous chronic angina*	54 (28·9)	72 (27·9)	82 (16·2)	208 (21·9)	<0·001
Symptom onset <1 week before admission*	96 (51·3)	136 (52·7)	314 (62·4)	546 (57·6)	=0·006
Event type:					
Unstable angina	43 (21·7)	54 (20·5)	107 (20·7)	204 (20·9)	NS
Infarction	155 (78·3)	210 (79·5)	408 (79·3)	773 (79·1)	
Complications (infarcts only)					
Uncomplicated	85 (54·8)	99 (47·1)	205 (50·1)	389 (50·3)	
Complicated	70 (45·2)	111 (52·9)	203 (49·9)	384 (49·7)	NS
†Site of infarction (Q wave infarcts only):					
Anterior	88 (62·0)	73 (39·0)	183 (49·7)	344 (49·4)	<0·001
Inferior	54 (38·0)	114 (61·0)	185 (50·3)	353 (50·6)	
Total	198 (20·2)	264 (27·0)	515 (52·8)	977 (100)	

*Missing: 28 cases.
†Excludes other or unknown sites and non-Q wave infarcts (n = 76).

Table 3 *Relation of smoking habits to peak increase cardiac enzymes in patients with myocardial infarctions*

Smoking habit	*SGOT (IU/l)*	*CK (IU/l)*	*LDH (IU/l)*
Never smoked	206 (n = 143)	1146 (n = 145)	939 (n = 142)
Ex-smoker	181 (n = 202)	1146 (n = 202)	869 (n = 200)
Current smoker	235 (n = 387)	1382 (n = 388)	952 (n = 386)
p	0·241	0·010	0·120

Significance based on Kruskal-Wallis one way analysis of variance. SGOT, serum glutamic oxaloacetic transaminase, CK, creatine kinase; LDH, lactate dehydrogenase.

never smoked, 515 (52·7%) current smokers, and the remaining 264 (27·0%) were ex-smokers. Information on length of time since they had stopped was available on all but 10 ex-smokers; 34·8% had given up within five years of attack, 37·4% had given up between five and 15 years, and the remainder more than 15 years before admission. The mean age of smokers was eight years lower than that of patients who had never smoked, and the mean age of ex-smokers was three years lower ($p < 0.001$). Concentrations of both total serum cholesterol and high density lipoprotein fraction were higher in patients who had never smoked. Smoking habits differed significantly between the sexes—34·6% of women and 12·7% of men had never smoked. There was also a significantly higher prevalence of hypertension among patients who had never smoked. When multiple logistic regression was used to correct differences in risk factors for differences in age between smokers and non-smokers, both sex and hypertension were still significantly associated with smoking status ($p < 0.001$) while cholesterol and high density lipoprotein fraction were not ($p = 0.263$ and 0·320 respectively).

Current smokers were less likely to have had chronic angina of effort before infarction (table 2) and a higher proportion of them had had symptoms for less than a week before admission, but when multiple logistic regression was used to correct for differences in age distribution, neither chronic angina nor rapid onset of symptom was associated with smoking status ($p = 0.581$ and 0·265 respectively). The proportion of patients whose first overt symptoms of coronary heart disease occurred within a week of admission was similar among non-smokers (51·3%) and ex-smokers (52·7%), but higher among current smokers (62·4%).

Smoking habits were not related to type of episode (unstable angina or infarction) and among patients with infarction they were not related to the occurrence of complications. However, among patients with infarctions there was a significant association between site of infarction and smoking habits; anterior infarction was more common in patients who had never smoked.

Among patients with myocardial infarction there was no relation between smoking habits and peak activities of serum glutamic oxaloacetic acid transaminase or lactic dehydrogenase. The peak concentration of creatine kinase was higher in current smokers (table 3).

Table 4 records the in-hospital complications and outcome in relation to smoking. Many patients had more than one complication. Patients who had never smoked had a higher risk of death and mechanical complications, notably cardiogenic shock. Rare complications in which there was no difference between smoking groups are omitted from the table. Two infrequent complications were associated with smoking status. Junctional rhythm, which occurred in 12 (1·2%) cases, was more common among patients who had never smoked (3·5%) than among current or former smokers (0·6%) ($p = 0.003$) and mitral incompetence was also more common in patients who had never smoked, with only one of the four cases occurring in current or ex-smokers ($p = 0.032$). Because smoking status and site of infarction were strongly associated we performed a logistic regression analysis to examine the effect of smoking on in-hospital end points independently of other factors.

Table 5 shows the relation of smoking habits to death, left ventricular failure, and mechanical complications, corrected for age and the presence of

Table 4 *Relation of smoking to in-hospital mortality and complications (number (%))*

	Smoking habit				
	Never smoked	*Ex-smoker*	*Current smoker*	*Total*	*p*
Died in hospital	33 (16·7)	19 (7·2)	28 (5·4)	80 (8·2)	<0·001
Cardiogenic shock	19 (9·6)	8 (3·0)	20 (3·9)	47 (4·8)	=0·002
LV failure	43 (21·7)	44 (16·7)	89 (17·3)	176 (18·0)	NS
Hypotension	12 (6·1)	7 (2·7)	24 (4·7)	43 (4·4)	NS
Ventricular fibrillation	10 (5·1)	19 (7·2)	35 (6·8)	64 (6·6)	NS
Any mechanical complication	64 (32·3)	57 (21·6)	111 (21·6)	232 (23·7)	=0·006
Any ventricular arrhythmia	16 (8·1)	26 (9·8)	54 (10·5)	96 (9·8)	NS
Supraventricular complications	17 (8·6)	27 (10·2)	47 (9·1)	91 (9·1)	NS
Atrioventricular block	16 (8·1)	14 (5·3)	32 (3·2)	62 (6·2)	NS

See text for definition complications. Information on complications was missing in one case. LV, left ventricular

Table 5 *Effects of smoking, age, and type of acute episode on inpatient outcome, assessed by logistic regression*

Effect of:	*Outcome* *Died in hospital*	*Cardiogenic shock*	*Any mechanical complication*
Current smoker			
Relative risk	1·04	1·71	1·35
p	0·896	0·221	0·140
Never smoked:			
Relative risk	1·92	2·48	1·25
p	0·043	0·042	0·332
Age.			
Relative risk	1·09	1·08	1·06
p	<0·001	<0·001	<0·001
Anterior M I.			
Relative risk	2·23	2·52	3·80
p	0·001	0·003	<0·001

Anterior infarction = 1; all other events = 0.

anterior myocardial infarction. Smoking habits were analysed as two separate variables: whether the patient had *ever smoked* and whether the patient was a *current smoker on admission*. The effect of each factor is presented as a relative risk and its associated probability. The relative risk for age although small is highly significant, since it represents the relative risk associated with a unit increase in age. All other relative risks are those associated with the presence of the factor. Patients who had never smoked had a higher mortality and a higher rate of left ventricular failure which were independent of their older age and higher prevalence of anterior myocardial infarction. In contrast, patients who were current smokers at time of admission were not at a significantly higher risk than ex-smokers.

Discussion

Cigarette smoking is a major risk factor for coronary heart disease and those who stop have a more favourable prognosis after myocardial infarction.[1] Pipe and cigar smoking are also associated with an increased coronary mortality,[2] although this effect may be less pronounced than with cigarette smoking.[2 3] Smoking may cause myocardial infarction not only by accelerating the development of atherosclerosis[4 5] but also by exerting thrombotic[6] or vasospastic[7] effects. The arrhythmogenic effect of smoking increases the risk of life threatening arrhythmias and sudden death. Myocardial infarction can occur in smokers with normal or nearly normal coronary arteries; this is a common finding in young, heavy smokers.[8]

Current smokers with a first acute coronary event in this study were younger and more likely to be male. They were less likely to have hypertension and they had lower concentrations of total and high density lipoprotein cholesterol.

In our patients, infarct size, estimated enzymatically, was larger in current smokers than in non-smokers, although this effect reached statistical significance only for creatine kinase. In patients with occlusion of the left anterior descending coronary artery, smoking had an independent adverse effect on left ventricular function.[9] This was attributed to a possible failure of development of collateral flow in smokers. Such a mechanism would also account for the larger infarcts seen in our patients.

Despite this, the outcome was better in smokers than non-smokers. This may be explained by the difference in distribution of site of infarction in the various groups. Different risk factor profiles may be responsible for different patterns of coronary disease[8] and we noted a significant association between site of infarction and smoking habits, with an excess of anterior infarctions among patients who had never smoked. One previous study noted a relation of site of infarction to smoking habits,[10] but the authors did not distinguish between non-smokers and ex-smokers and they reported an excess of inferior infarctions in current smokers rather than in current smokers and ex-smokers. The greater proportion of inferior infarctions in smokers suggests a greater prevalence of left coronary disease in non-smokers and, possibly, a true smoking related effect on the right coronary artery. Furthermore, right coronary occlusion may result not only in damage to the left ventricle but also to the right. Right ventricular infarction may not, however, have the same adverse prognostic implications as left ventricular infarction and this may explain the apparently contradictory findings of a better prognosis for smokers in the face of a larger infarct size.[11]

In contrast to the studies cited above, when we entered smoking habits as two variables—whether the patient had *ever smoked* and whether they were a *current smoker*—into a logistic regression we were able to distinguish between these two features, at the same time correcting the analysis for age and presence of anterior infarction, both of which were related to smoking habits. The analysis showed first that the effect of smoking on prognosis is independent of both age and infarction site and secondly that the effect of smoking on prognosis is not the result of a better prognosis in current smokers, but of a worse prognosis in patients who have never smoked. Ex-smokers and current smokers had a similar prognosis, despite the fact that current smokers had the largest and ex-smokers the smallest infarctions, estimated enzymatically.

It is important to bear in mind that the patients studied had survived long enough to be admitted to coronary care. The apparent difference in prognosis between non-smokers and current or ex-smokers may have arisen because a larger proportion of smokers died before admission to hospital. There are no published data to confirm this hypothesis. Similarly, the adverse in-hospital prognosis associated with anterior infarction[10] may be the explanation for the higher death rate in non-smokers.

There are important differences between smokers and non-smokers in the manifestations of acute coronary heart disease. Apart from the difference in aetiology, smokers and non-smokers show differences not only in size and site of infarction, but also in in-hospital prognosis.

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Relation of infarct site to 15 year prognosis in patients who survived for 28 days after a first myocardial infarction

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SUMMARY Six hundred and eighty four patients (629 men), all aged under 60 years, who had survived for 28 days after a first acute myocardial infarction were studied to determine the influence of the site of infarction on long term prognosis. The infarct site was not significantly related to age nor to extent of infarct at the time of the acute episode. Mechanical complications were more common in patients with anteroseptal infarctions, while atrioventricular conduction disturbances were more commonly found in those with inferior infarction. The site of infarction was not related to smoking habits or angina before the infarction or at 2 year follow up.

Life table methods did not show any relation between infarction site and morbidity or mortality either two years or 15 years after the initial infarction.

Studies of in-hospital and short term outcome in patients with myocardial infarction have shown that prognosis is poorer in anterior myocardial infarction than in inferior infarction, even when size of infarction is controlled for.[1-3]

The relation of site to long term prognosis has been less frequently examined, and although several studies have shown a worse long term outcome in anterior infarction[4-7] others have shown no difference.[8-10]

We examined the relation of site to 15 year morbidity and mortality in patients aged < 60 who survived for at least 28 days after a first acute myocardial infarction.

Patients and methods

This study is based on long term follow up study of two groups of patients who survived for at least 28 days after a first myocardial infarction when they were < 60. Between 1965 and 1975 inclusive only men were recruited; between 1978 and 1982 inclusive both sexes were included.

Myocardial infarction was diagnosed when there was typical cardiac pain at rest with abnormal Q waves or a twofold or greater increase in serially measured serum glutamic oxaloacetic acid transaminase, creatine kinase, and lactate dehydrogenase, or both.

The site of infarction was classified as anteroseptal if electrocardiographic changes were seen in some or all of leads V1–V4, anterolateral if changes were in some or all of leads V3–V6, combined anteroseptal and anterolateral with changes in V1–V6, or inferior if the changes were noted in II, III, and aVF with or without changes in V4–V6.

In-hospital complications were recorded according to a standard protocol which defined a total of 34 complications. Hemiblocks and premature atrial or ventricular contractions were not rated as complications because these had not been recorded with sufficient detail in some of the earliest cases admitted to the study.

The presence of angina of effort before infarction was recorded as were smoking habits before infarction. Chronic angina was regarded as being present before infarction only if it started three months or more before. Patients were classified as non-smokers if they had never smoked as many as one cigarette per day regularly, ex-smokers if they had smoked less than one cigarette per day for at least three months before infarction, and current smokers if they had regularly smoked at least one cigarette per day in the three months before admission.

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Table 1 *Relation of infarction site to age and to size and severity of infarction*

	ASMI + ALMI	*ASMI*	*ALMI*	*IMI*	*Total*
Total cases	27 (4·0%)	237 (34·5%)	55 (8·1%)	367 (53·5%)	686
Mean (SD) age (yr)	51·74 (6·65)	50·84 (6·71)	53·76 (5·18)	50·87 (6·60)	51·04 (6·55)
Kruskall-Wallis ANOVA, Age by site: $p = 0·274$					
Peak increase in SGOT (Iu/l):					
Mean	182·0	184·1	137·8	168·4	171·5
SD	130·7	121·9	80·8	122·7	120·1
No of cases*	19	180	46	292	537
Kruskall-Wallis ANOVA, SGOT by site: $p = 0·154$					
Prevalence of complications (%)	59·3	41·7	36·4	35·9	38·9
$\chi^2 = 7·0$, df = 3, $p = 0·071$.					

*149 cases missing.
Infarct site: ASMI, anteroseptal; ALMI, anterolateral; IMI, inferior

Angina and smoking habits were recorded at two year follow up outpatient visit. Primary cigar and pipe smokers and cigarette smokers who changed to cigar or pipe smoking after infarction were classified as current smokers.

We recorded the date and mode of death for those who died and the date that survivors were last seen. Vascular deaths were subdivided into reinfarction with shock, congestive heart failure, or sudden death (death within one hour of onset of terminal symptoms). The date of occurrence of any further acute episodes of coronary heart disease was noted. Acute episodes were defined as either reinfarction, as defined above, or unstable angina characterised by typical cardiac pain at rest and confirmed by serial ST or T wave changes in the electrocardiogram but with no increase or a less than a twofold increase in the concentration of cardiac enzymes.

Categorical data were compared by the χ^2 test and differences in the distributions of metric variables between infarct topography groups were tested by the Kruskall-Wallis one-way analysis of variance by ranks. This latter test was chosen because both age and cardiac enzyme activities were not normally distributed. Life table methods were used to estimate survival functions and differences in survival experience between groups were tested by the logrank test. Because few patients were followed for more than 15 years, this study is confined to fifteen year life table morbidity and mortality rates.

Results

Six hundred and eighty six patients fulfilled the entry criteria. In two further cases left bundle branch block precluded identification of the infarction site and these patients were dropped from the analysis. Fifty five patients were women. Table 1 shows the relation between site and age, severity of infarction, and peak concentration of glutamic oxaloacetic acid transaminase. Patients with anterolateral infarctions showed the smallest rise in serial concentrations of glutamic oxaloacetic acid transaminase, and patients with other anterior infarctions showed the highest, but a one way analysis of variance did not reach statistical significance.

Table 2 *Relation of infarction site to smoking habits before and after infarction*

	ASMI + ALMI	*ASMI*	*ALMI*	*IMI*	*Total*
Preinfarction smoking habit.					
Never smoked	3 (11·1%)	23 (9·7%)	4 (7·3%)	37 (10·1%)	67 (9·8%)
Ex-smoker	5 (18·5%)	60 (25·3%)	13 (23·6%)	70 (19·1%)	148 (21·6%)
Current smoker	19 (70·4%)	154 (65·0%)	38 (69·1%)	260 (70·8%)	471 (68·7%)
		$\chi^2 = 4·0$, df = 63, $p = 0·686$			
Smoking at 2 year follow up.					
Never smoked	1 (4·3%)	18 (9·0%)	3 (5·9%)	34 (10·9%)	56 (10·9%)
Ex-smoker	4 (17·4%)	46 (23·1%)	11 (21·6%)	56 (17·9%)	117 (20·0%)
Current stopped	11 (47·8%)	80 (40·2%)	20 (39·2%)	123 (39·3%)	234 (39·9%)
Current, smoking	6 (26·1%)	53 (26·6%)	16 (31·4%)	99 (31·6%)	174 (29·7%)
Ex, restarted	1 (4·3%)	2 (1·0%)	1 (2·0%)	1 (0·3%)	5 (0·9%)
Missing:					
Dead	3	22	3	26	54
Lost to follow up	0	11	1	15	27
No 2 yr follow up	2	7	1	12	22
		$\chi^{2*} = 5·37$, df = 9, $p = 0·801$			

*Excludes ex-smokers who restarted (n = 5)
Infarct site: ASMI, anteroseptal; ALMI, anterolateral; IMI, inferior.

Table 3 *Relation of infarction site to pre-infarction and post-infarction angina*

	ASMI + ALMI	*ASMI*	*ALMI*	*IMI*	*Total*
Total cases	27 (4 0%)	237 (34·5%)	55 (8 1%)	367 (53·5%)	686
Preinfarction angina:					
Present (%)	18·5	18 4	22 2	18·8	18·9
Resolved 2 yr (%)	50 0	51·4	70·0	50 0	52 3
Absent (%)	81 5	80·3	77·8	80 9	21·7
Appeared 2 yr (%)	25·0	25·9	12·5	20 3	21 7
Relation of site to:					
Pre-infarction angina	p = 0·766 (NS)				
Post-infarction angina	p = 0 850 (NS)				
Change in angina	p = 0·764 (NS)				

Details of information on 2 year follow up missing from table 2. Infarct site: ASMI, anteroseptal; ALMI, anterolateral, IMI, inferior

One or more complications were present in 38·9% of patients. There were complications in 59·3% of patients with infarctions extending through both anterior sites but the overall χ^2 value was of borderline significance ($p = 0·071$). Mechanical complications—left ventricular failure, cardiogenic shock and hypotension—showed a significant relation to site of infarction ($p < 0·001$); they were most common in combined anteroseptal and anterolateral infarcts (37·0%) and anteroseptal infarcts (19·0%), while anterolateral and inferior infarcts had similar rates (10·9% and 11·5% respectively). Atrioventricular blocks were significantly related to site, with 42 of 45 cases occurring in inferior infarction ($p < 0·001$). No other complications showed a significant relation to infarct site. The site of the infarct was not related to age.

Because of the influence of subsequent smoking habits on prognosis after myocardial infarction[8] and of the influence of pre-infarction or post-infarction angina on subsequent clinical course,[5] we examined the relation of these factors to infarct site. There was no association between site and either smoking habits on admission or change in smoking habits over two year follow up (table 2).

Similarly, there was no association between site and either pre-infarction angina or change in anginal symptoms over two year follow up (table 3). Prognosis was assessed by life table methods over a fifteen year period. There were 340 patients available for calculation of five year event rates, 211 at ten years, and 60 at 15 years.

Table 4 shows the life table rates for 15 year endpoints in the study group as a whole and within the subgroups for infarct site. Patients with combined anteroseptal and anterolateral infarctions were excluded from morbidity and mortality calculations because there were so few. Life table mortality was 61·4% at fifteen years, with a 33·1% rate of non-fatal acute episodes of coronary heart disease. At fifteen year follow up coronary heart disease mortality was 56·6%. There was no difference in event rates between the groups with different infarct sites. Several further analyses were carried out to examine differences in prognosis in relation to site of infarction. A cause specific mortality analysis was performed to test for higher rates of sudden death or of fatal reinfarction with other causes controlled. Neither sudden death nor fatal reinfarction was significantly more common in any topographical group. Among patients experiencing a subsequent episode of coronary heart disease, there was no association between site and type of episode (infarction or unstable angina). We also examined mortality and morbidity in the first two years after discharge to determine whether early prognosis was related to site. Once again, no significant relation emerged between site and event rates.

Discussion

Long term prognosis after myocardial infarction has been related to several variables, including age,[1 7 10] sex,[1 10] hypertension,[7] smoking,[8] diabetes,[7] previous

Table 4 *Relation of site to 15 year prognosis (%)*

	ASMI	*ALMI*	*IMI*	*Total*	*p*
15 year mortality	60 7 (5 1)	68·1 (11 4)	60 3 (4·2)	61 4 (3 0)	0·739
15 year non-fatal acute CHD	37·7 (5·1)	28 4 (9·2)	31 3 (3·9)	33 1 (2·8)	0·509
15 year fatal CHD	59·4 (5·9)	59 2 (14·1)	54 6 (4·7)	56 6 (3·6)	0 492
15 year sudden death	36 6 (5 9)	45·0 (17·8)	31·1 (4·3)	34 1 (3·42)	0 405

Results are mean (SEM). Infarct site: ASMI, anteroseptal; ALMI, anterolateral; IMI, inferior. CHD, coronary heart disease.

history of acute coronary heart disease,[4 5 7] pre-infarction angina,[5 7] infarct size,[1 7 9] cardiomegaly,[10] cardiac failure at the time of infarction,[1 4 5] ejection fraction,[5 9] and arrhythmias, both atrial[7] and ventricular,[4 5 7] and the extent of coronary artery disease.[5]

Although site of infarction seems to be important in determining in-hospital prognosis,[2] even allowing for the larger size of anterior infarction,[3] its effect on long term prognosis is less clear.[4-7] In part this disparity may result from the inclusion in other studies of patients with previous infarction[4] and those who did not survive the in-hospital phase of their illness. To our knowledge, ours is the longest follow up study of the relation of infarct site to subsequent outcome. It is, furthermore, a useful study of the natural course of the disease, since few of the patients underwent coronary artery bypass surgery or routine treatment with β blockade after infarction.

Risk factors of patients with anterior and inferior infarctions were identical, which is consistent with the findings of Taylor *et al*, who noted the same extent of coronary disease in patients with myocardial infarction irrespective of the site of the infarct.[9] Necrosis of the left ventricular muscle rather than the thinner right ventricular muscle and complications such as acute regional dilatation, left ventricular aneurysm, and myocardial rupture seem to be more common with anterior infarction than inferior infarction. This may account for the larger enzymatically estimated infarct size in anterior infarction reported by some[3] and for the higher in-hospital mortality of patients with anterior infarction. Even among 28-day survivors, patients with anterior infarctions had higher rates of mechanical complications.

Furthermore, we were unable to show a difference in the pattern of subsequent episodes of acute coronary heart disease for up to 15 years after myocardial infarction that was related to site of infarction. Not only were total mortality rates the same, but the subsequent prevalence of angina and the incidence of both fatal and non-fatal episodes of acute coronary heart disease were also similar. Sudden death rates were also no different.

Although a difference in mortality might be expected on the basis of differing infarct sizes, and could be explained by more left ventricular damage in anterior infarction, once healing has taken place and the groups with a poorer prognosis have been removed by their higher early death rate, infarct site seems unimportant in determining outcome after a first episode of acute coronary heart disease.

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Does β adrenergic blockade influence the prognostic implications of post-myocardial infarction exercise testing?

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SUMMARY The influence of β blockade on the ability of ST depression, during pre-discharge exercise testing, to predict coronary anatomy and subsequent complications was studied in 300 consecutive post-infarct patients, 125 of whom underwent cardiac catheterisation. At the time of exercise 62 patients were taking a β blocker. The exercise test had a higher sensitivity in predicting multivessel disease in patients who were not taking β blockers than in patients who were (95% *v* 76%). β Blockade did not, however, influence the ability of the test to identify patients at risk of subsequent cardiac events (sensitivity 84% and 85% respectively).

These results suggest that it is not necessary to stop treatment with β blockers before pre-discharge exercise testing of patients who have had an acute myocardial infarction.

The value and limitations of pre-discharge exercise testing in predicting the extent of coronary artery disease[1–3] and in identifying both high and low risk patients after acute myocardial infarction are well established.[4–6] When exercise testing is carried out for diagnostic purposes, however, it has been suggested that β adrenergic blockade may reduce the ability of the test to identify patients with clinically significant coronary artery disease.[7–9] After myocardial infarction many patients are treated with β blockers but, to date, the impact of β blockade on the results of post-infarct exercise testing has not been studied.

We investigated whether treatment with β blockers influenced the ability of pre-discharge exercise testing to identify those with multivessel disease or those at risk of subsequent cardiac events after a myocardial infarction.

Patients and methods

PATIENTS

Over an 18 month period all patients aged less than 66 years with electrocardiographic and enzymatic evidence of acute myocardial infarction who survived to discharge from our coronary care unit were considered for pre-discharge exercise testing.[10] We did not test patients with uncontrolled angina pectoris or cardiac failure, those with other serious cardiac or non-cardiac disease which would limit ability to exercise or affect short term prognosis, and patients who were unwilling to perform an exercise test.

ELECTROCARDIOGRAPHIC CHANGES

A diagnosis of myocardial infarction was based on the development of new Q waves or the evolution of ST-T wave changes on the electrocardiogram in association with either a typical history of chest pain persisting for at least 30 minutes or a rise in the concentration of aspartate transaminase or lactic dehydrogenase to twice the upper limit of normal. The site of infarction was determined from the resting electrocardiogram in the following way: in anterior infarction changes were seen in leads V1–V5, in lateral infarction in leads V6, I, and aVL, and in inferior infarction in leads II, III, and aVF.

All exercise tests were performed on a treadmill according to a modified Naughton's protocol.[11] A 12 lead electrocardiogram, blood pressure, and heart rate were recorded at rest and at one minute intervals throughout the test. After the test, data were recorded every two minutes up to 10 minutes.

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Exercise stopped at 18 minutes (equivalent to seven multiples of resting energy expenditure) or earlier if the patient developed limiting symptoms, ventricular arrhythmias, profound ST segment depression (>4 mm), or a fall in systolic blood pressure >20 mm Hg. ST segment depression ⩾1 mm at 80 ms from the J point of the QRS complex on three consecutive beats, in lead groupings remote from the site of infarction was taken to indicate reversible ischaemia and disease in vessels other than the infarct related vessel—that is multivessel disease. The absence of ST depression on exercise was taken to imply disease confined to the infarct site only.

CARDIAC CATHETERISATION

All patients with exercise induced ST segment depression, symptoms suggestive of angina pectoris, and those aged less than 45 years were offered cardiac catheterisation. Selective coronary arteriography was performed six weeks after discharge from hospital by the Judkins technique. The catheter data were analysed without knowledge of the electrocardiographic data. A reduction in luminal diameter of ⩾50% at angiography was regarded as indicating haemodynamically significant stenosis.[2 12] Patients were designated as having single vessel disease if a significant stenosis was found in only one of the three main coronary arteries and as having multivessel disease if there was a significant stenosis in more than one of the three main arteries or a stenosis in the left main coronary artery.

The exercise test results were related to findings at coronary arteriography: remote ST depression in association with multivessel disease signified a true positive result and ST depression in association with disease confined to the infarct related vessel signified a false positive result. Single vessel disease confined to the infarct related vessel with no associated ST depression indicated a true negative result, while multivessel disease with no associated ST depression indicated a false negative result.

CLINICAL END POINTS

All patients were followed up in our cardiology clinic for a mean (SD) of 12 (3) months. During this time the occurrence of the following events was noted: (*a*) death; (*b*) recurrent myocardial infarction; (*c*) heart failure (this was defined as the need to introduce or increase antifailure treatment); (*d*) severe angina pectoris (this was defined as the need to introduce specific antianginal medication in addition to *β* blockers); metoprolol (100 mg twice daily) was prescribed routinely to all patients after completion of their exercise test unless clinically contraindicated; (*e*) coronary bypass grafting or percutaneous transluminal angioplasty (these were performed for angina pectoris that was unresponsive to medical treatment or for asymptomatic disease of the left main coronary artery (one patient)).

Some patients had more than one cardiac event during the follow up period. Therefore, the number of patients who suffered one or more cardiac events was noted. As death and reinfarction are the two most important cardiac events the number of patients with these major complications was also noted.

Exercise test results were related to clinical outcome. In this context, ST depression in a patient who experienced at least one subsequent cardiac event indicated a true positive result while ST depression in a patient who did not experience any cardiac event during the follow up indicated a false positive result. A true negative result indicated a patient who had neither ST depression on exercise nor any subsequent cardiac events, while a false negative result indicated a patient who did not have ST depression on exercise but did experience at least one cardiac event on follow up.

STATISTICAL ANALYSIS

Student's *t* test was used to assess differences between the means of independent observations. The χ^2 test was used to assess differences between proportions. A p value <0·05 was regarded as statistically significant. Values are given as mean (SD).

Results

Three hundred and fifty patients were considered for exercise testing over an 18 month period. Fifty did not perform a pre-discharge exercise test: 38 because of heart failure, seven because of the presence of other serious medical conditions, three because of

Table 1 *Background clinical variables and exercise test variables (mean (SD)) in patients treated with β blockers and those who were not*

	β Blocker (n = 62)	*No β blocker (n = 238)*	*95% Confidence intervals*
Age (yr)	53 (8 2)	53 (4·6)	−3 8 to +4·2
Males	45 (72%)	176 (74%)	−10% to +14%
Norris index	4 2 (1 4)	4 5 (1 4)	−0 7 to +1 3
AST (SI units)	149 (88)	171 (86)	−2 to +46
LDH (SI units)	1518 (847)	1534 (728)	−14 to +46
Infarct site:			
Anterior	27 (44%)	100 (42%)	−16 to +16
Inferior	28 (45%)	120 (50%)	−15 to +20
Other	7 (11%)	18 (8%)	−25 to +18
Q wave infarction	47 (76%)	167 (70%)	−14 to +10
Exercise duration (min)	10·4 (3 3)	10·7 (3 2)	−0·8 to +1 4
ST depression (mm)	2·2 (0 9)	2 6 (1 1)	−0 4 to +0 6

AST, Aspartate aminotransferase, LDH, lactic dehydrogenase.

Table 2 *Prognostic implications of ST depression induced during exercise testing when cardiac events were grouped together and when patients were subdivided on the basis of treatment or with β blockers at the time of exercise*

	True +	*True −*	*False +*	*False −*
β Blockers (62)	16 (26%)	32 (52%)	11 (18%)	3 (5%)
No β blockers (238)	95 (40%)	90 (38%)	36 (15%)	17 (7%)

	β Blocker (n = 62) (%)	*No β blocker (n = 238) (%)*	*95% Confidence intervals %*
Sensitivity	84	85	−17 to +19
Specificity	74	71	−20 to +14
Predictive accuracy	77	77	−10 to + 9
Positive predictive value	59	73	− 6 to +34
Negative predictive value	91	84	−10 to +20

practical difficulties, and two refused to exercise. Of the 300 patients who were exercised 158 had ST segment depression on exercise. The mean age of the exercised patients was 53 years (range 28–65 years). The male/female ratio was 5·4 : 1.

β BLOCKADE

At the time of exercise 62 of the 300 patients were already taking a β blocker; 42 patients had been started on a β blocker in the early stages of acute myocardial infarction, 13 had been taking β blockers before infarction, and seven had been started on treatment after their infarct because of angina pectoris (four) or hypertension (three). Of the 158 patients with ST depression, 27 were taking a β blocker at the time of exercise and 131 were not. In those who were being treated with β blockers and those who were not age, sex, Norris index, enzymatically estimated infarct size, and infarct site were similar (table 1). The two groups exercised for a similar length of time (10·4 (3·3) and 10·7 (3·2) minutes respectively) and had a similar degree of ST depression (2·2 (0·9) and 2·6 (1·1) mm respectively). Thirty seven per cent of those on β blockers and 45% of those who were not developed angina pectoris on exercise testing ($\chi^2 = 1·1$; NS).

CLINICAL OUTCOME

During the follow up period 131 (44%) of the 300 patients had at least one cardiac event. Twenty four suffered recurrent myocardial infarction and 11 of them died. A further three patients died without evidence of reinfarction. Thus 27 patients died or had reinfaction. One hundred and fifteen (38%) developed angina pectoris, 38 (13%) developed cardiac failure, and 39 patients (13%) had coronary bypass surgery or percutaneous angioplasty. Some patients are included in more than one category.

RELATION OF EXERCISE TEST RESULTS TO OUTCOME

One hundred and fifty eight of the 300 patients had ST segment depression on exercise. Table 2 shows that when all cardiac events were grouped together β adrenergic blockade at the time of exercise testing did not influence the ability of the test to identify patients at risk of subsequent complications. When cardiac events were studied individually or when the two major events (death and reinfarction) were taken together it was again apparent that β blockade did not influence the test sensitivity (table 3).

RELATION OF EXERCISE TEST RESULTS TO CORONARY ANATOMY

A total of 125 patients underwent cardiac catheterisation, 90 because of exercise induced ST segment depression and 35 for other reasons—symptoms suggestive of myocardial ischaemia (29) or age less than 40 years (six). Seventy three (81%) of patients with ST segment depression and eight (23%) of 35 patients without ST depression had multivessel disease ($\chi^2 = 62·0$, $p < 0·001$). Twenty seven of the 125 catheterised patients were taking a β blocker at the time of exercise. Twenty one (77%) of the 27 patients taking β blockers and 60 (61%) of the 98 who were not had multivessel disease. Five (19%) of the 27 patients taking β blockers had false negative exercise tests compared with three (3%) of the 98 not taking β blockers (χ^2, 6·1; $p < 0·05$). As a result, the

Table 3 *Sensitivity of ST depression in predicting individual cardiac events when patients were subdivided on the basis of treatment with β blockers at the time of exercise*

	β Blockers (n = 62)			*No β blockers (n = 238)*			
	STD (n = 27)	*No STD (n = 35)*	*Sensitivity (%)*	*STD (n = 131)*	*No STD (n = 107)*	*Sensitivity (%)*	*95% Confidence intervals*
Death	1	0	100	9	4	69	−28 to +34
MI	3	0	100	18	3	86	− 5 to +29
HF	3	0	100	26	9	74	−11 to +41
Angina	10	3	75	85	17	83	− 7 to +33
Surgery	8	0	100	28	3	90	− 2 to +20
Death/MI	3	0	100	20	4	83	−12 to +32

HF, heart failure; death/MI, death or myocardial infarction; STD, ST segment depression on exercise.

Table 4 *Ability of ST depression induced by exercise to predict multivessel disease when patients were subdivided on the basis of treatment with β blockers at the time of exercise*

	True +	*True −*	*False +*	*False −*
β Blockers (27)	16 (59%)	4 (15%)	2 (7%)	5 (19%)
No β blockers (98)	57 (58%)	23 (23%)	15 (15%)	3 (3%)

	β Blocker (n = 27) (%)	*No β blocker (n = 98) (%)*	*95% Confidence intervals %*
Sensitivity	76	95	0 to +38*
Specificity	67	61	−35 to +47
Predictive accuracy	74	82	− 1 to +17
Positive predictive value	89	79	− 7 to +27
Negative predictive value	44	88	+ 9 to +79*

*p < 0 05.

result, the exercise test had a higher sensitivity (95% *v* 76%; χ^2, 4·25; p < 0·05) and a higher negative predictive value (88% *v* 44%; χ^2, 5·06; p < 0·05) in predicting coronary anatomy in patients who were not taking β blockers than in those who were (table 4). The test had a similar specificity, predictive accuracy, and positive predictive value in the two groups of patients.

RELATION OF CORONARY ANATOMY TO PROGNOSIS

Fourteen of the 125 catheterised patients died or reinfarcted. The three patients who were taking β blockers and had such major events had both ST depression on exercise and multivessel disease, as did 10 of the 11 patients who were not taking β blockers and who died or reinfarcted (figure). None of the catheterised patients with single vessel disease had a major complication.

Discussion

β Adrenergic blocking agents can reduce or delay the onset of angina pectoris and ST segment depression on exercise testing.[7-9] Consequently, if β blockers are used after myocardial infarction, either as antianginal treatment or exclusively for secondary prevention, most physicians avoid prescribing them before the patient has a pre-discharge exercise test. However, many patients will have been receiving β blockers before their infarct and such treatment is often continued while the patient is in the coronary care unit. In addition, some patients may be started on a β blocker while in the coronary care unit, either to limit infarct size,[13 14] or for angina pectoris. Stopping such treatment before exercise testing is hazardous, particularly after myocardial infarction, because of the risk of a rebound effect.[13] As a result many patients perform their pre-discharge post-infarct exercise tests while they are taking β blockers. Until now the impact of β blockade on the results of pre-discharge exercise testing had not been studied.

In the current study the sensitivity of pre-discharge exercise testing in detecting multivessel disease was lower in patients taking β blockers (76%) than in those who were not (95%). Our data seem to be at variance with those of Marcomichelakis *et al*, who studied patients with suspected coronary disease who had not suffered an infarct before and after the introduction of β blockade.[9] They found that oxpren-

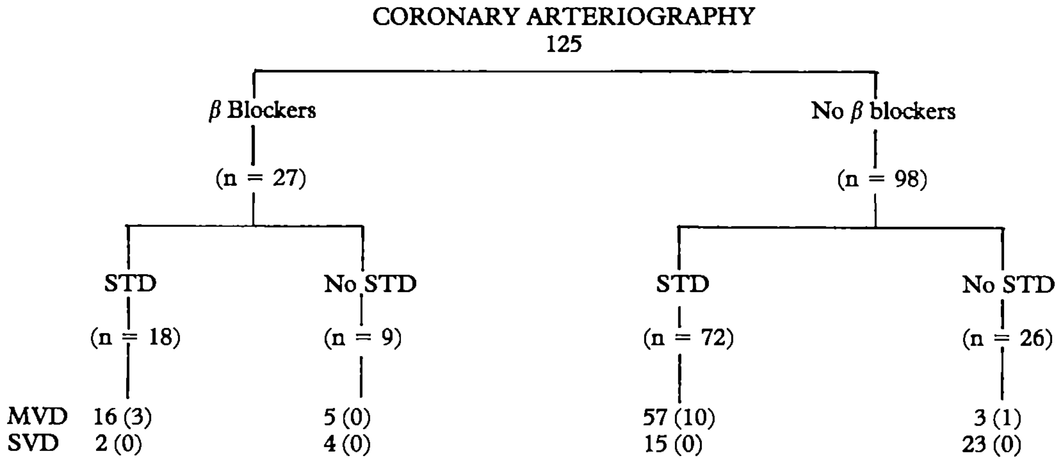

Figure *Ability of ST depression induced by exercise testing to predict multivessel disease and major complications (death or reinfarction) when patients were subdivided on the basis of treatment with β blockers at the time of exercise. (Numbers in parentheses are those who died or reinfarcted.) MVD, multivessel disease; SVD, single vessel disease; STD, ST depression on exercise testing.*

olol increased the specificity of the exercise test, abolishing some false positive results, without reducing the sensitivity. No patient with coronary artery disease and a positive exercise test before treatment with β blockers had a negative test when oxprenolol was introduced. However, two factors should be noted when these results are compared with ours. In the study by Marcomichelakis *et al* the patients performed symptom limited exercise tests and in these patients treatment with β blocker did delay the onset of ST depression.[9] In the current study the patients performed submaximal exercise tests. Thus it is likely that the patients treated with β blockers had a higher incidence of false negative exercise tests than those who were not treated with β blockers. This is because β blockade abolished or delayed the onset of ST depression. This is consistent with the results of both Fox *et al*[8] and Ho *et al*.[15] In these studies patients without a recent history of myocardial infarction performed maximal exercise tests on and off β blockers. In both studies β blockade was associated with increased exercise duration and delay in onset of ST depression. In the study by Ho *et al* 14 patients with ST depression before β blockade developed equivocal tests while they were treated with β blockers. Fox *et al* found that 16 patients had complete and 16 had incomplete abolition of exercise induced ST depression when they were treated with β blockers. Thus it seems that on symptom limited exercise testing β blockade can abolish false positive exercise tests and reduce or delay the onset of ST depression in patients with multivessel disease. These data are consistent with our arteriographic data which showed a higher incidence of false negative tests in patients treated with β blockers (19%) than in those who were not (3%). It seems likely that β blockade prevented the development of ST depression on exercise in some of our patients.

The presence of β blockade at the time of exercise testing did not seem to limit the ability of the test to identify those patients who were at risk of subsequent cardiac events. When all cardiac events were grouped together, exercise testing was equally sensitive in identifying patients at risk of subsequent cardiac events in patients treated with β blockers and those who were not. This also appeared to be true when cardiac events were studied individually. However, the number of events in each category is small and as a result the confidence intervals are wide. As far as we know the influence of β blockade on the prognostic implications of pre-discharge exercise testing has not been evaluated before.

Why did β blockade seem to have a different effect on the ability of exercise testing to predict coronary anatomy than it did on the ability of the test to predict prognosis? This question is important because multivessel disease is recognised as one of the most useful predictors of prognosis after myocardial infarction. It may be that although multivessel disease does imply increased risk after infarction, it is still a non-specific marker.[16] In the current study a large proportion of such patients had no subsequent cardiac event during the follow up period. This finding is consistent with the results of the Coronary Artery Surgery Study[18] and with the data of workers who studied the prognostic importance of multivessel disease after acute myocardial infarction.[16-18] It is well recognised that the patients with the worst prognosis after acute myocardial infarction are those with severe left ventricular dysfunction who are unable to perform a pre-discharge exercise test.[4 6] Among patients with preserved left ventricular function who are able to perform an exercise test it seems likely that those with most severe ischaemia on exercise testing, in addition to those with multivessel disease, are also the group who are at greatest risk of subsequent cardiac events. Given that β blockade can delay or abolish myocardial ischaemia, as manifest by ST segment depression on exercise, it is also probable that exercise induced ST depression will be abolished in those with least severe ischaemia, even if they have multivessel disease. In contrast, if exercise induced ischaemia is so severe that it is not abolished by β blockade, it seems reasonable to expect that such a patient would have a high risk of subsequent cardiac events. Thus β blockade may in fact have filtered out patients with less severe ischaemia on exercise. It was to be expected, therefore, that while β blockade might decrease the accuracy of submaximal exercise testing in identifying patients with multivessel disease it was less likely to reduce the ability of the test to identify patients at risk of subsequent cardiac events. This is borne out by the fact that none of the patients treated with β blockers who had negative exercise tests and multivessel disease died or reinfarcted.

CLINICAL IMPLICATIONS

These data have important implications for the assessment of patients after myocardial infarction. It seems that β blockade reduces the ability of pre-discharge exercise testing to identify patients with multivessel disease. Despite this effect the test does not seem to lose its prognostic powers and is still able to identify patients at risk of subsequent cardiac events. Since this is the chief reason for performing the test we feel that it is not necessary to stop treatment with β blockers before pre-discharge exercise testing of patients who have had an acute myocardial infarction.

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Cardiac surgery for patients aged 65 years and older: a long term survival analysis

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SUMMARY Between January 1973 and December 1984, 562 patients aged ≥65 had cardiac surgery at Papworth Hospital. Most had mitral or aortic valve replacements (coronary artery bypass grafting was not introduced for this age group at Papworth until 1977). The overall operative mortality, defined as death within thirty days or death before leaving hospital, was 7·3%. There were no early deaths in patients undergoing coronary artery bypass grafting surgery. Questionnaires sent to general practitioners in East Anglia traced 86·0% of the patients who survived to leave hospital. The longer term survival rates for all patients were 88·0%. (95% confidence interval (CI) 85 to 91) at one year and 74·4% (95% CI 69 to 79) at five years. The rates for those patients who survived the initial few months were 96·3% (95% CI 94 to 98) at one year and 81·5% (95% CI 77 to 86) at five years and these rates were no different from those in the general population aged ≥65.

Although cardiac operations are increasingly performed on elderly patients there is little published evidence on the long term survival. Most centres believe that patients should not be denied the benefit of cardiac surgery simply on the grounds of age, though this was not always the case. An editorial in the *British Medical Journal* in 1968 expressed doubts about the surgical treatment of valvar heart disease in the elderly[1] and in 1979 Kirklin *et al* questioned the advisability of coronary artery surgery in patients aged ≥70[2]. But by 1980 the value of cardiac surgery in the treatment of heart disease in the elderly was being increasingly accepted.[3 4]

The term "elderly" is difficult to define. During the past two decades it has been used to describe different age groups—sixty was considered old by Oh *et al* in 1973[4] but later reports have defined 70 as elderly.[5 6] None the less, the age of retirement and the pensionable age for men in the United Kingdom is 65 and this was the age group chosen for a specific report by the Coronary Artery Surgery in the United States Study.[7]

For these reasons we chose to review all patients over 65 undergoing cardiac surgery but we also evaluated those over 70 as a separate group.

The proportion of elderly patients undergoing cardiac surgery at Papworth Hospital has increased from 11 in 1973 (8·1% of operations) to 96 (16·8%) in 1984. This had risen further to 120 (20·5%) in 1985 but this group was not included in the survival figures because of the lack of long term data. Figure 1 shows the percentages of operations in patients ≥65 each year from 1973 to 1985.

Several centres have reported on cardiac surgery in elderly patients but most have concentrated on perioperative mortality and there have been few reports of long term follow up. We report our experience over the twelve years from January 1973 to December 1984.

Patients and methods

All 562 "elderly" patients who underwent cardiac surgery at Papworth Hospital from January 1973 to December 1984 were included in the review. The patients were studied in two age groups—those aged between 65 and 69 years at the time of operation (group 1) and those aged ≥70 in group 2 (321 (57·1%) were male and 241 (42·9%) were female).

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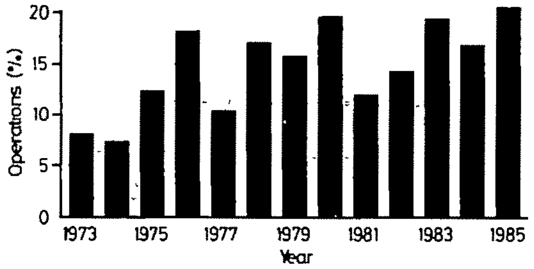

Fig 1 *Operations by year 1973–1985.*

Table 1 shows the distribution of patients by age, sex, and type of operation.

The term "elective" was applied to those patients who were placed on the routine waiting list to await admission for operation and did not include patients who had operations soon after infarction or those with unstable angina. Patients with impaired left ventricular function were not excluded.

Most patients (62·1%) needed operation because of valvar heart disease. Early on in the study many patients with valve disease did not have coronary angiography before operation but in those who did, it was our policy to undertake grafting only if stenoses were severe—that is >75% reduction in luminal diameter. We prefer to use bioprosthetic valves in this age group and to treat these patients with anticoagulants for only 8–12 weeks, unless the left atrium is large or there is atrial fibrillation. If a mechanical valve was used we preferred to use a Björk Shiley prosthesis.

We first used coronary artery bypass grafting for patients aged ⩾65 in 1977. In both age groups (⩾65–69 and ⩾70) more men were treated with coronary bypass surgery and for both sexes this operation was performed in more patients in the 65–69 age group than in those aged ⩾70.

The operations were all performed at moderate hypothermia (30–32°C). Myocardial protection was initially by profound local cardiac hypothermia, and cardioplegia was added in 1976. Hospital records provided basic data on the study population and early survival rates. We sent questionnaires to the general practitioners of all those patients who survived to leave hospital to determine longer term survival.

We excluded two groups of patients from the survival analysis: the 73 whom we failed to trace and the 18 patients that we knew had died but for whom we did not have a date of death. Complete follow up data was available for 471 patients from one to 12 years.

STATISTICAL ANALYSIS

We used life table analysis of annual intervals to assess survival and we compared the two age groups by the Lee-Desu statistic.[8] For multivariate analysis of survival we used the Cox proportional hazard model.[9] Proportions were compared by the χ^2 statistic and we used multiway analysis of variance to adjust for background factors.

From the mortality statistics for England and Wales published in 1982[10] we calculated the expected survival rates for the study population and we compared these with the actual rates. 1982 was the year closest to the midpoint of the 12 years 1973–1984 which included a breakdown of mortality per 1000 population by age and sex.

Results

CHANGES IN CLINICAL PRACTICE

Table 2 gives a breakdown of data on elderly patients by type of operation before and after 1980. The number of coronary artery bypass grafting operations carried out after 1980 increased considerably. Even though those given coronary artery bypass grafts tended to be younger ($p < 0{\cdot}001$), two way analysis of variance showed that, allowing for type of operation, the mean age of patients increased over time ($p < 0{\cdot}001$).

Operations in the category "other" included aortic dissections, aneurysms, acquired ventricular septal defects, congenital defects, and complicated valve procedures.

Table 1 *Patients by age group and type of operation (number (%))*

	Group 1 (<70)		*Group 2 (>70)*		
Operation	*Male*	*Female*	*Male*	*Female*	*Total*
Valve	101 (46)	97 (66)	70 (70)	81 (86)	349 (62)
CABG	81 (37)	20 (14)	12 (12)	4 (4)	117 (21)
Both	25 (11)	9 (6)	15 (15)	2 (2)	51 (9)
Other	13 (6)	21 (14)	4 (4)	7 (7)	45 (8)
Total	220 (100)	147 (100)	101 (100)	94 (100)	562 (100)

CABG, coronary artery bypass graft.

Table 2 *Patients by operation type and period (number (%))*

Operation	*Before 1980*	*Mean Age (yr)*	*After 1980*	*Mean Age (yr)*
Valve	154 (80)	68·3	195 (53)	70·0
CABG	9 (5)	66·0	108 (29)	67·7
Both	6 (3)	69·7	45 (12)	68·8
Other	24 (12)	67·1	21 (6)	68·7
Total	193 (100)	68·1	369 (100)	69·1

CABG, coronary artery bypass grafting.

Table 3 *Early mortality by age group and type of operation (% and proportion)*

Operation	*Group 1 (<70)*	*Group 2 (≥70)*	*All ages*
Valve	4 (7/198)	8 (12/151)	5 (19/349)
CABG	0 (0/101)	0 (0/16)	0 (0/117)
Both	18 (6/34)	6 (1/17)	14 (7/51)
Other	32 (11/34)	36 (4/11)	33 (15/45)
Overall	6·5 (24/367)	8·7 (17/195)	7·3 (41/562)
Emergency	19·2 (5/26)	21·7 (5/23)	20·4 (10/49)

CABG, coronary artery bypass grafting.

EARLY MORTALITY

Early operative mortality was defined as death within 30 days of operation or death before leaving hospital—40 of the 41 early deaths occurred in hospital. Early mortality for cardiac surgery patients of all ages at Papworth between the years 1973 to 1984 was 4·8%. In the elderly it was 7·3% (95% CI 5·1 to 9·5)—6·5% in group 1 and 8·7% in group 2.

Table 3 shows the operative mortality by type of operation and age group for all 562 elderly patients and for 49 patients who had emergency operations. Analysis of variance shows that once operation type is taken into account, being aged less than 70 and having an operation after 1980 are both associated with a small (3·0%) but not statistically significant benefit. The sex of the patient had no influence. Of the ten early deaths after emergency operation, six were in patients who had operations in the "other" category, and the remainder occurred in patients with valve disease.

Figure 2 shows that the overall operative mortality for elderly patients fell from 36·4% in 1973 to 5·2% in 1984. The operative mortality after elective surgery alone had fallen from 33·0% in 1973 to 1·2% in 1984. In the more recent cohort of patients whose operations took place between 1980 and 1984, there were 232 in group 1 and 137 in group 2. The mean (SD) overall operative mortality in this period was 5·7% (21) for all patients and 4·0% for patients who had elective operation. The early mortality for valve replacement alone in this five year period was 5·1%—2·1% for the younger age group and 8·1% for the over 70s (p = 0·12).

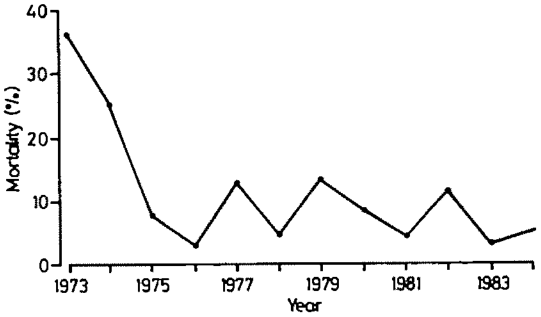

Fig 2 *Early mortality 1973–1984.*

SURVIVAL

Figures 3–6 show the survival statistics for the elderly patients who died in hospital or were later traced by questionnaire.

The survival rates for all 471 elderly patients in whom follow up information was complete were 88·0% (95% CI 85 to 91) at one year and 74·4% (95% CI 69 to 79) at five years (fig 3). The older age group fared only slightly worse than the younger group (p = 0·1). The ten year survival rate was 46·5% (95% CI 33 to 61) for all elderly patients—50·1% in group 1 and 39·7% in group 2. The sex of the patient was not an important factor in predicting survival whereas the type of operation was (p < 0·001). (fig 4)

Table 2 shows that only the group with valvar disease provides sufficient data for a comparison of long term survival in patients operated on in different periods. Figure 5 shows the survival rates for the cohorts of patients undergoing valve surgery before and after 1980. The survival of patients operated on after 1980 was slightly better but the difference was not statistically significant (p = 0·67).

A multifactorial analysis (Cox proportional hazard model) with stratification by operation showed that the relative annual risk of death associated with being over 70 at operation was 1·45, (95% CI 0·97 to 2·16), that for operation after 1980 was 0·79 (95% CI 0·52 to 1·21), and that for being female was 0·95 (95% CI 0·65 to 1·39). These figures support the findings in the single factor analysis—that age may have a slight adverse effect, with a possibility of some improvement in survival over time, and that the sex of the patient has little or no influence.

Coronary artery bypass grafting was first performed on patients aged ≥65 in 1977 and since then there have been no operative deaths from this procedure. Longer term survival data are available

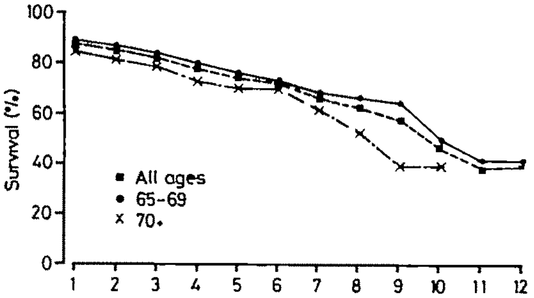

Fig 3 *Survival by age of patient.*

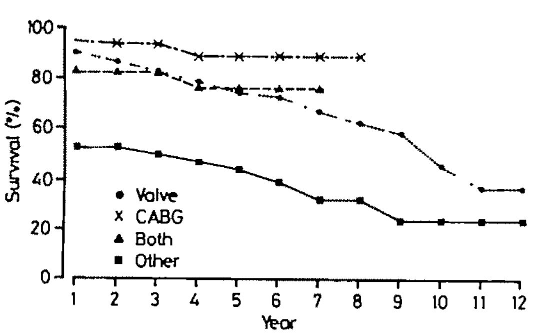

Fig 4 *Survival by type of operation.*

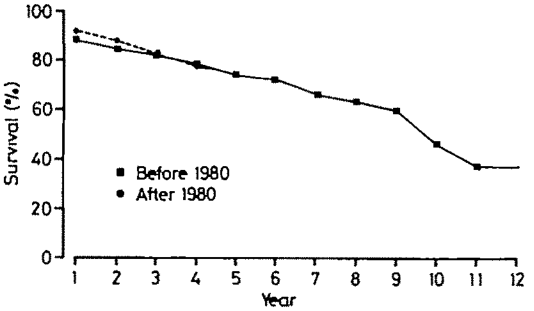

Fig 5 *Survival by period of operation.*

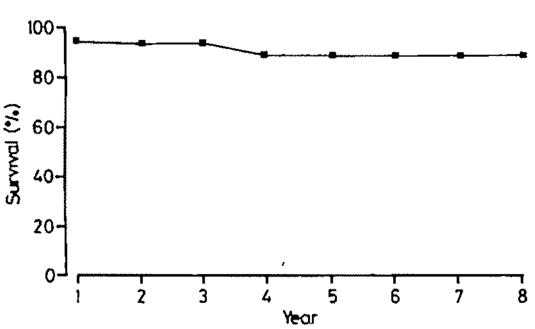

Fig 6 *Survival of patients with coronary artery bypass grafts.*

for 100 out of the 117 patients who had coronary artery bypass grafting (fig 6). The 17 patients who were not traced by questionnaire were excluded from the survival figures. The survival rates were 95·0% (95% CI 91 to 99) at one year falling to 89·0% (95% CI 81 to 97) at eight years. Of those elderly patients who had an operation between 1977 and 1980 only three have been lost to follow up, and all of those traced are alive.

To assess whether the 73 patients we could not trace were less likely to have survived, we compared their population structure with that of the 489 patients whom we did trace. Similarly, to determine whether the 18 patients whose date of death was unknown were less likely to have survived as long we compared them with the 81 whose date of death was known. The 73 patients whom we failed to trace were no different in age, sex, or type of operation than the patients who were traced—but a higher proportion of these patients had been operated on before 1980. In terms of age, sex, operation type, or period of operation (before or after 1980) the population structure of the 18 patients whose date of death was unknown was no different from that of the 81 whose date of death was known.

When we compared the expected and actual survival rates in the study population, we found that the expected one year rate was 96·4% and the actual rate was 88·0%. For the five year rates the corresponding figures were 80·1% expected compared with 74·4% actual. But after the 41 early deaths were excluded from the study population we found that the actual one and five year rates for the remaining patients were 96·3% (95% CI 94 to 98) and 81·5% (95% CI 77 to 86) respectively. So the survival rate of patients who survived the first months after operation was similar to that of people aged ≥65 in the general population.

Discussion

Although increasing age is usually associated with a higher operative mortality after cardiac surgery[11] we found an operative mortality and long term survival that would be acceptable for any major surgical procedure. The consistently low early mortality rate for elective surgery and the increasing numbers of patients being operated on each year mark cardiac surgery as being one of the most successful and beneficial forms of operation in the elderly.

The operative mortality for all procedures during the 12 year period (7·3%) resembles that reported by the Coronary Artery Surgery Study (5 2%),[7] Bessone *et al*, (3·7%)[6] McCallister *et al* (6%)[12] and Gann *et al* (8%)[13] for a much shorter time span. The presence of untreated coronary artery disease in patients with valve disease, before the subsequent introduction of coronary artery bypass grafting, and improved myocardial protection and the increasing willingness of cardiologists to recommend an increasingly safe procedure to patients earlier in the course of their illness may have all contributed to a general improvement in early mortality.

In the years 1973–1975 early mortality after elective surgery improved considerably and when the changing mix of operations was allowed for we found that in percentage terms the improvement since 1975 was small. However, this should be viewed against the much larger numbers of elderly patients now passing through the unit, the increase in the average age of patients over time, and the broader selection criteria applied to elderly patients. An early mortality rate of 4·3% was reported from Papworth Hospital in 1978 for valve replacement in 68 patients over the age of 65 from 1973 to 1976.[14] The overall mortality of 5·0% for 1980 to 1984, of 186 patients having valve replacement shows that the expansion of activity in the unit has been managed safely.

An emergency operation will always carry a greater risk than an elective procedure and this is true for the elderly. The early mortality associated with the very small numbers of emergency cases at Papworth has varied widely over the years. Thus although a 1·2% mortality for elective surgery was achieved in 1984, the overall rate was 5·1% because early mortality for emergency operation was 30% in the same year (3/10 cases), and while there were no deaths after the three emergency cases in 1982, the mortality after elective operation that year was 12·0%.

Thus the early mortality in elderly patients continues to reflect the pattern of cases presenting and the tendency in recent years to operate on patients who used to be considered to be too ill for operation.

Mortality from coronary artery bypass grafting is universally less than that associated with valve replacement and although the zero operative mortality we report has rarely been matched,[11] most centres have quoted a variable early mortality for this procedure (Knapp *et al*[15] 1·1%, Coronary Artery Surgery Study[7] 5·2%, McCallister *et al*[12] 6·0%). This level of operative mortality combined with excellent long term prospects for these patients—almost 90% of all patients traced were alive at eight years—should guarantee the place of coronary artery bypass grafting in the treatment of ischaemic heart disease in the elderly, with the same selection criteria being applied as for patients under 65 years old.

The move away from the purely symptomatic treatment of heart disease in the elderly will continue and although any improvement in quality of life these patients may attain awaits formal documentation, an afternoon in the outpatient clinic reassures us that the gains are considerable.

We thank the general practitioners of East Anglia and their staff for their invaluable assistance in completing questionnaires and tracing patients and Mrs Rosemary Martin for her help with data processing.

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Lack of effect of warfarin on the restenosis rate or on clinical outcome after balloon coronary angioplasty

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SUMMARY Between September 1985 and April 1987, 110 consecutive patients who had successful coronary angioplasty were included in a randomised prospective controlled evaluation of the effects of warfarin on restenosis. The warfarin (n = 56) and the control (n = 54) groups were not different in terms of age, sex, previous coronary bypass surgery or coronary balloon angioplasty, severity of symptoms, and frequency of multivessel disease or of total coronary occlusions. Warfarin was started on the day of the procedure and the dosage was adjusted to maintain the thromboplastin international normalised ratio $\geqslant 2{\cdot}5$. One hundred and five (96%) of the patients were given verapamil and other antianginal drugs were prescribed as needed. Low molecular weight dextran and heparin were given during the procedure and heparin was continued for 24 hours in all patients. One hundred and eight (98%) of patients were followed up clinically after a median of five months (range 1–20). Eighty five (77%) had follow up angiography at five months. In the warfarin group symptoms improved in 46 (85%) patients by at least 1 angina class and 31 (57%) were symptom free; the exercise test remained positive in 20 (36%) patients and the angiographic restenosis rate was 25% per lesion and 29% per patient. There were no major bleeding complications. In the control group 46 (85%) patients were improved by at least 1 angina class and 31 (57%) were symptom free; the exercise test was positive in 11 (21%) patients and the angiographic restenosis rate was 33% per lesion and 37% per patient. Although the incidence of angiographic restenosis tended to be lower with warfarin, none of these differences was significant.

These data suggest that the combination of verapamil and warfarin, in the absence of aspirin, is not significantly better than verapamil alone in preventing symptom recurrence or angiographic restenosis after coronary angioplasty.

Restenosis, usually occurring during the first three to six months after coronary balloon angioplasty, remains one of the main limitations of the technique.[1 2] Although several risk factors associated with an increased rate of recurrence have been identified,[1 3 4] our understanding of the underlying pathophysiological mechanisms remains incomplete, and no drug regimen has yet been shown consistently to affect the occurrence of restenosis.[5–7]

As it is currently understood, restenosis is a response to balloon induced arterial injury and is determined by multiple elements. Mechanical factors (elastic recoil of the dilated arterial segment, medial dissection, and intimal flap formation), haemostatic factors (thrombus formation and platelet deposition), and fibromuscular proliferation all occur and interact to induce restenosis.[8–10]

There is good experimental and clinical evidence that early local thrombus formation is a key element in restenosis.[11 12] Because of these data, and despite a previously reported negative result,[13] we undertook a prospective randomised controlled study of the effects of warfarin on the clinical outcome and angiographic restenosis rate after angioplasty.

Patients and methods

PATIENTS AND MEDICATION

Between September 1985 and April 1987, 155 consecutive patients underwent coronary artery balloon angioplasty at our hospital. The initial success rate was 76% for 140 stenoses and 47% for 15 occlusions—113 patients had a successful and

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uncomplicated procedure (target lesion(s) with < 50% residual stenosis). One hundred and ten of these patients were randomly assigned to receive either warfarin and verapamil or verapamil alone after the procedure. Table 1 gives the baseline clinical data of both groups. Only lesions causing $\geq$ 70% stenosis were considered for angioplasty. All types of angioplasty were included—that is stenosis or occlusion, single or multivessel procedures, native vessels or vein grafts, primary stenosis or restenotic lesions (table 2). Twelve patients were included twice and two patients were included three times. During the study period, three patients were excluded before randomisation (one with a recent cerebrovascular accident that contraindicated the use of anticoagulants, one taking long term warfarin because of atrial fibrillation, and one who was successfully treated with streptokinase for recurrent chest pain with ST segment elevation a few hours after angioplasty).

All patients were given heparin 10 000 IU intravenously before angioplasty together with an infusion of low molecular weight dextran. Heparin was continued for 24 hours after the procedure, until the arterial sheath was taken out. Verapamil was started on the day of the procedure. In the anticoagulated group warfarin was begun on the evening of the angioplasty day. Dosage was adjusted to obtain a thromboplastin international normalised ratio of $\geq$ 2·5.[14] Verapamil and warfarin were continued either for six months or until a follow up angiogram was obtained. No antiplatelet agents were prescribed at discharge, but one patient in the warfarin group and six patients in the control group were given aspirin at some time during the follow up period. Aditional antianginal treatment such as nitrates or β blockers were given as required. There was no difference in the postoperative management of patients undergoing angioplasty of single or multiple lesions.

Table 1 *Clinical and angiographic data for warfarin and control groups*

Data	*Warfarin (n = 56)*	*Control (n = 54)*
Number	56	54
Mean age (SD)	56 (9)	57 (10)
Sex (% male)	88	83
CCS class 3 or 4	37 (66)	42 (77)
Unstable angina	6 (11)	13 (24)
Previous AMI	22 (39)	18 (33)
Previous CABG	7 (13)	11 (20)
Previous PTCA	13 (23)	9 (17)
Positive stress test	39/44 (89)	32/39 (82)
Multivessel disease	26 (46)	27 (50)

Except where indicated numbers in parentheses are percentages.
CCS, Canadian Cardiovascular Society; unstable angina, rest pain together with transient electrocardiographic changes; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty

Table 2 *Angioplasty data for warfarin and control groups*

	Warfarin (n = 56)	*Control (n = 54)*
Lesion/patient (successfully treated)	1 2	1 3
Multilesion procedure	10 (18)	10 (19)
Multivessel procedure	3 (5)	4 (7)
Total occlusion*	4 (7)	2 (4)
Restenosis*	6 (11)	9 (17)
Target:		
LMS	0	1 (2)
LAD	33 (57)	32 (57)
LCX	7 (12)	6 (11)
RCA	13 (22)	14 (25)
VG	5 (9)	3 (5)

*Present in at least one of the target lesions for a given procedure.
Numbers in parentheses are percentages.
LMS, left main stem coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery, RCA, right coronary artery, VG, vein graft

FOLLOW UP

Most patients were followed up as outpatients at the National Heart Hospital. For those who were unable to return, information was obtained from the referring physician whenever possible. Anticoagulation was monitored in anticoagulant clinics with regular checks of the international normalised ratio. Clinical follow up data, stress testing, and follow up angiograms were generally obtained three to nine months after angioplasty, or earlier if symptoms recurred or became worse.

END POINTS OF STUDY

Clinical state, the response of the ST segment to exercise, and the angiographic appearance of the angioplasty site were analysed at follow up. Before angioplasty and at follow up we used the Canadian Cardiovascular Society (CCS) grading system for subjective assessment of anginal symptoms. Unstable angina was defined as rest pain together with reversible electrocardiographic changes. The exercise test was symptom limited and done according to the modified treadmill Bruce protocol with monitoring of 12 electrocardiogram leads. ST segment depression of $\geq$ 1 mm developing in at least one lead during or after exercise was regarded as a positive test. Angiographic restenosis was considered to be present when there was $\geq$ 50% reduction in luminal diameter estimated from at least two projections at the site of the previous angioplasty.

We compared the results in the warfarin and the control groups by Student's t test for continuous variables and by the χ^2 test for discrete variables. Differences of $p < 0{\cdot}05$ were considered to be statistically significant.

We calculated that for a power of 0·75 and a significance level of 0·05, we would need 54 patients in each group to show a 50% reduction in the restenosis rate.

Results

The two groups (warfarin and control) were similar for all the clinical and procedural variables tested (tables 1 and 2).

CLINICAL OUTCOME

At follow up we had subjective information on anginal symptoms for 108 (98%) of 110 patients (96% of the warfarin group and 100% of the control group). In the warfarin group (median follow up six months, range 1–18 months), 46 (85%) of 54 patients had improved by ⩾ 1 Canadian Cardiovascular Society angina class, and 31 (57%) were symptom free. Two patients (4%) were in class 4 and no patient had unstable angina. There were no major bleeding complications in the warfarin group. The results were similar for the control group (median follow up five months, range 1–20 months) where 46 (85%) of 54 were improved and 31 (57%) were symptom free. One patient (2%) was in class 4 and two had unstable angina (4%).

STRESS TESTING

Results of stress testing at follow up were available for 81 (74%) of 110 patients (75% of the warfarin group and 72% of the control group). In the warfarin group, 15 (36%) of 42 patients had an appreciable depression of the ST segment with exercise, and in 16 (38%) of 42 chest pain developed. The test was symptom limited and patients reached a median of Bruce protocol stage 3 (range 1–5). In the control group, eight (21%) of 39 patients had significant ST segment depression with exercise and in 12 (31%) chest pain developed. They reached a median of stage 3 of the Bruce protocol (range 0–5). None of these differences was statistically significant.

ANGIOGRAPHY

Angiographic follow up was obtained in 85 (77%) of 110 patients (75% of the warfarin group and 80% of the control group). After a median follow up of five months (range 1–19 months) in the warfarin group the restenosis rate was 29% per patient (12 of 42) and 25% per lesion (12 of 49). In the control group, the median follow up was five months (range 1–20 months), the restenosis rate per patient was 37% (16 of 43), and per lesion 33% (18 of 54).

During the follow up period in the warfarin group eight (15%) patients underwent a repeat angioplasty and two (4%) had elective coronary artery bypass grafting. Corresponding figures in the control group were nine (17%) and one (2%) respectively. There were no deaths in either group during the follow up period.

Discussion

Despite our initial hypothesis that warfarin would favourably affect clinical and angiographic outcome after coronary balloon angioplasty, we found that our results confirmed a previous finding[13] and did not show that oral anticoagulation had a significant effect on medium term results. This is the first comparison of the effects of anticoagulation with a control group that essentially had no antiplatelet treatment. Angiography showed that there was a trend towards a reduction in the restenosis rate for the patients in the warfarin group, and it could be argued that a larger study population might have shown a significant difference or have retrospectively identifed a subset in whom warfarin reduced the incidence of restenosis. However, in the absence of any difference in the subjective evaluation of anginal symptoms or electrocardiographic changes during stress testing, such an angiographic trend is difficult to interpret. The angiograms were analysed according to current clinical practice and the percentage reduction in the diameter at the angioplasty site was estimated visually. The angiographic views were standarised as far as possible and the films interpreted without knowledge of the individual's clinical condition. The cut off value of 50% taken to represent significant restenosis is widely accepted[10] but arbitrary. Our study was limited by the lack of quantitative computer assisted analysis of the angioplasty site.[15]

Compliance with the anticoagulation regimen after angioplasty has been reported to be less than ideal.[13] Because the patients in this series were regularly followed in anticoagulant clinics, compliance with treatment was good.

The timing of anticoagulation treatment in relation to angioplasty is probably an important factor, and in the present series there was a gap of 24–48 hours between the end of heparin administration after angioplasty and the establishment of effective oral anticoagulation. In view of the currently available data[11 12] such an interruption is probably undesirable, since the thrombosis and platelet deposition that contribute to restenosis may well occur at a very early stage. At the time when the study was designed it was thought that withdrawing the arterial sheath under full anticoagulation would cause problems, but experience with patients undergoing intracoronary stenting[16] has shown that it is feasible with few complications.

The best drug regimen for preventing restenosis after angioplasty remains to be determined. Thornton *et al* reported that warfarin was no better than aspirin, and showed that aspirin was better than warfarin for patients with a long history of angina.[13] Fleck *et al* showed that interruption of aspirin treatment during follow up was associated with an increased risk of restenosis,[17] but their conclusions have been challenged by others.[10] Calcium channel blockers are widely prescribed after angioplasty, but currently there are no data to support this practice.[5 6]

Aspirin together with dipyridamole has recently been shown to reduce occurrence of acute closure after angioplasty,[18] and a similar combination is also known to be effective in maintaining patency in saphenous vein grafts.[19] Antiplatelet agents are currently being evaluated for their ability to prevent restenosis in several continuing controlled clinical trials.[7]

The effect of individual compounds on restenosis should be tested first. But the success of combination treatments with oral anticoagulants and one or several antiplatelet agents together may prove to be more important if the current interest in intravascular stenting devices[16] is maintained. This is because the initial thrombogenic properties of the currently used metallic stents means that empirical vigorous anticoagulation together with antiplatelet medication has been used during the first months after implantation.[16 20] If the restenosis rate is lower that that expected with conventional balloon angioplasty, the benefits derived from the mechanical support and those obtained by the drug regimen alone will have to be determined.

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Haemodynamic response to dopexamine hydrochloride in postinfarction heart failure: lack of tolerance after continuous infusion

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SUMMARY Dopexamine is a new vasodilator with a combination of dopamine receptor and β_2 adrenoreceptor agonist properties. Its haemodynamic effects were assessed after dose titration and during infusion for up to 24 hours in 15 patients with heart failure after acute myocardial infarction. At the initial titration a dose of 1 μg/kg/min produced a 25% decrease in the systemic vascular resistance index and a 32% increase in cardiac index. Stroke volume index and heart rate increased by 23% and 9% respectively. Left ventricular filling pressures and mean blood pressures were not affected. The short term effects were well sustained during the long term infusion and tolerance did not develop.

Administration of dopexamine to patients with heart failure after acute myocardial infarction augments cardiac performance at rest.

Heart failure is a common complication after acute myocardial infarction with a bad prognosis.[1-3] Treatment is given to improve the depressed left ventricular function and thereby reduce symptoms, to improve exercise capacity, and to improve outcome. In the short term, improvement of cardiac function is most important. This can be achieved either by stimulating the cardiac contractile reserve[4-7] and/or by reducing preload and afterload.[8-10] Potent inotropic agents may, however, cause further cardiac metabolic deterioration by increasing oxygen demand[10 11] and their usefulness may be limited by tachycardia and induced arrhythmias.[12] Reduction of raised systemic vascular resistance is haemodynamically helpful to the failing heart, and vasodilator treatment has gained acceptance in the management of pump failure in patients with acute myocardial infarction.[9 13] Intravenous vasodilators with a rapid onset of action and short half life are better in the acute stage of heart failure.

Dopexamine, a novel substance derived from dopamine, has the properties of both a postjunctional dopamine receptor agonist and a β_2 adrenoreceptor agonist.[14 15] Stimulation of these receptors by dopexamine induces renal and mesenteric vasodilatation and peripheral vasodilatation particularly in skeletal muscle. The main haemodynamic effects of dopexamine as demonstrated in studies of animals,[16] volunteers and patients with chronic heart failure[17-20] are an increase in cardiac output and ejection fraction, a fall in system vascular resistance, and a mild positive inotropic effect. There is also indirect evidence of a diuretic effect equal to that of equivalent doses of dopamine. In addition to the above direct, receptor mediated pharmacological effects dopexamine is a potent, competitive inhibitor of the neuronal reuptake of catecholamines (uptake 1).[21]

We studied the haemodynamic effects and safety of dopexamine after dose titration and during the first 24 hours of treatment in patients with acute left ventricular failure after acute myocardial infarction. We also studied whether tolerance had developed by repeating the dose titration after the end of the infusion.

Patients and methods

PATIENTS

We studied 15 patients (eight men, seven women; mean age 66 years, range 45–75). Table 1 shows data on the patients, the infarct size and location, the time between admission and haemodynamic recordings, and the current treatment. Two patients (cases 2 and 9) had a history of heart failure. All patients had a

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Table 1 *Patient characteristics*

Patients	*Sex*	*Peak ASAT (μkat/l)*	*Peak CK (μkat/l)*	*Site of infarction*	*Previous infarction*	*Previous angina*	*Other diseases*	*Treatment before admission*	*Interval between admission and haemodynamic recording (h)*
1	M	8·05	60·0	Inf (T)	+	+	Hypertension	Atenolol Frusemide	50
2	F	6·65	64·0	Ant (T)	−	−	—	—	19
3	F	7·0	43·0	Ant (T)	−	+	—	Nitrates	43
4	F	6·3	50·0	Lat (T)	−	−	—	—	30
5	M	5·15	31·0	Inf (S)	−	−	—	—	27
6	M	7·7	63·0	Inf (T)	−	−	Rheumatoid arthritis	—	32
7	F	1·54	6·8	Ant (S)	+	+	—	Timolol Frusemide	49
8	M	4·14	28·4	Inf (T)	−	−	Hypertension	Thiazides	43
9	M	3·56	9·0	Inf (T)	−	−	Claudicatio	Digoxin Frusemide	50
10	F	7·05	42·0	Ant (T)	−	−	—	—	48
11	M	1·4	12·5	Inf (T)	+	−	Hypertension	Pindolol	47
12	F	1·08	4·2	Ant (S)	−	+	Hypertension	Verapamil Thiazides	48
13	M	2·23	12·2	Ant (T)	−	−	—	—	46
14	M	4·65	32·7	Inf (T)	−	+	—	—	45
15	F	8·25	63·0	Ant (T)	−	−	—	—	36

ASAT, aspartate aminotransferase; CK, creatine kinase; Ant, anterior; Inf, inferior; Lat, lateral; (T), transmural; (S), subendocardial. Normal values for ASAT ≤ 0·7, CK ≤ 2·9 (female), ≤ 2·4 (male) μkat/l.

recent myocardial infarction as shown by symptoms, enzyme and electrocardiographic changes. All patients also had signs of cardiac failure such as dyspnoea, a third heart sound, basal rales, respiratory rate over 20 beats/min, or a chest radiogram that was compatible with left heart failure and required diuretics (frusemide) after admission. They were all haemodynamically stable and in sinus rhythm.

Whenever possible no medication other than the trial treatment was given during the study. No medication was given within two hours of the start of the infusion, and patients who had received β adrenoreceptor antagonists within 48 hours of the study were excluded. Vasodilating agents were not given after admission.

The protocol was approved by the medical ethics committee of the Karolinska Hospital and all patients gave their informed consent.

HAEMODYNAMIC MEASUREMENTS

Twelve to 50 hours after admission to the coronary care unit each patient had a right heart catheterisation with a balloon tipped thermodilution Swan-Ganz catheter which was floated into the pulmonary

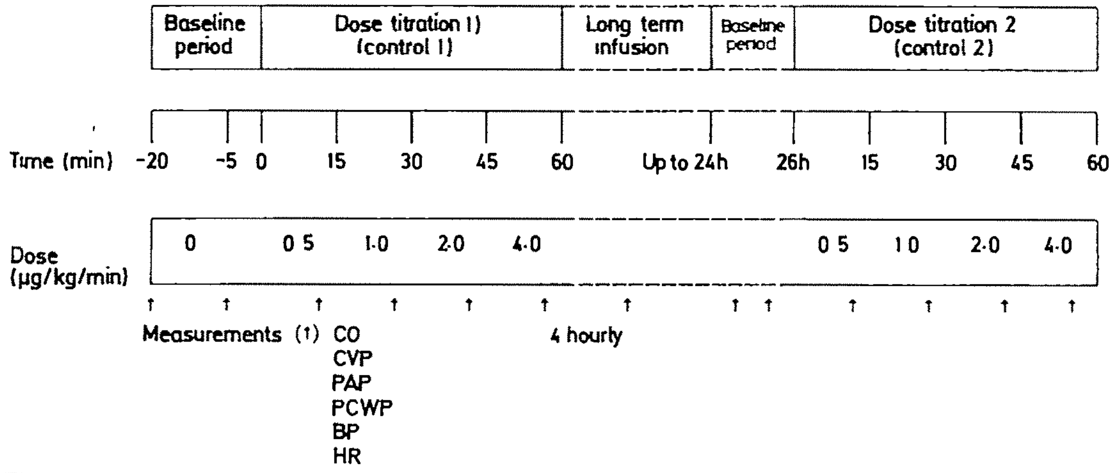

Fig 1 *Study design and measured variables in patients with heart failure after acute myocardial infarction. CO, cardiac output; CVP, central venous pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; BP, blood pressure; HR, heart rate.*

Table 2 *Haemodynamic data from the initial dose titration (phase 1)*

Haemodynamic variable	*Infusion rate (µg/kg/min)* 0	0·5	1·0	*Standard deviation*	*Significance (p)*	*LSD (0·05)*
Heart rate (beats/min)	79	81	86	3·51	$< 0·001$	2·97
Systolic blood pressure (mm Hg)	116	121	122	5·68	$< 0·05$	4·80
Diastolic blood pressure (mm Hg)	72	71	72	4·77	NS	4·03
Mean blood pressure (mm Hg)	87	88	88	4·61	NS	3·90
Systolic pulmonary artery pressure (mm Hg)	34	35	37	2·18	$< 0·01$	1·84
Diastolic pulmonary artery pressure (mm Hg)	17	16	17	1·28	NS	1·08
Mean pulmonary artery pressure (mm Hg)	22	22	23	1·40	NS	1·18
Pulmonary occluded pressure (mm Hg)	15	14	15	1·78	NS	1·91
Central venous pressure (mm Hg)	6	6	6	0·774	NS	0·654
Cardiac output (l/min)	3·68	4·22	4·91	0·317	$< 0·001$	0·268
Cardiac index (l min^{-1}m^{-2})	2·01	2·31	2·66	0·159	$< 0·001$	0·135
Stroke volume index (ml beat^{-1}m^{-2})	25·6	28·6	31·5	2·25	$< 0·001$	1·90
Systemic vascular resistance index (units/m^{-2})	41·6	36·1	31·3	3·71	$< 0·001$	2·99
Pulmonary vascular resistance index (units/m^{-2})	3·55	3·25	2·92	0·412	$< 0·05$	0·441
Left ventricular stroke work index (gxm/m^2)	24·5	28·2	31·0	3·71	$< 0·01$	3·14

LSD, Least significant difference.

artery. All measurements were made with the mid-axillary line as the zero reference level and with the patient in a supine position. Right atrial and pulmonary artery pressures were monitored continuously. Cardiac output was measured three times by a WTI holland Mc 401 thermodilution cardiac output computer. Left ventricular filling pressures were measured as pulmonary artery diastolic pressures if this was within ± 3 mm Hg of the pulmonary capillary wedge pressure. The heart rate was monitored from a continuously recorded electrocardiogram. Peripheral blood pressure was measured by sphygmomanometer cuff. Vascular resistance, stroke volume, and stroke work were calculated by conventional means.

DRUG ADMINISTRATION

This was an open study with three phases (fig 1).

Phase 1.—A dose titration at infusion rates of 0·5, 1·0, 2·0, and 4·0 µg/kg/min. The dose was increased every 15 minutes until an adequate clinical and haemodynamic response was obtained.

Phase 2.—A 24 hour continuous infusion with a dose that satisfied one of the following criteria: an increase of $> 30\%$ in cardiac output or a decrease of $> 30\%$ in mean pulmonary wedge pressure or pulmonary diastolic pressure. During the 24 hour infusion period the dose of dopexamine was increased or reduced according to the clinical condition of the patient.

Phase 3.—Control readings were taken two hours

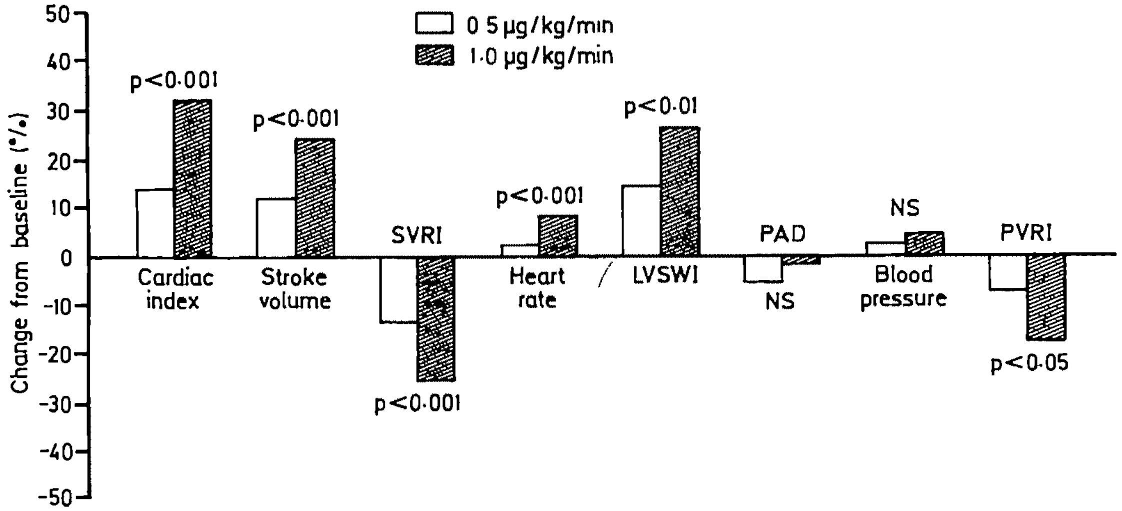

Fig 2 *Effects of dopexamine hydrochloride 0·5 and 1·0 µg/kg/min on haemodynamic variables during the initial dose titration (percent change from control). SVRI, systemic vascular resistance index; LVSWI, left ventricular stroke work index; PAD, pulmonary artery diastolic pressure; PVRI, pulmonary vascular resistance index.*

Table 3 *Haemodynamic data from the long term infusion (phase 2)*

Haemodynamic variable	*Control*	*Time into infusion* 4	8	12	20	24	*Standard deviation*	*Significance*	*LSD (0·05)*
Heart rate (beats/min)	76	90	90	89	91	93	4·44	<0·001	3·80
Systolic blood pressure (mm Hg)	123	133	131	129	124	125	6·31	<0·001	5·41
Diastolic blood pressure (mm Hg)	73	77	76	76	71	75	3·96	<0·01	3·39
Mean blood pressure (mm Hg)	90	95	94	93	88	92	4·05	<0·001	3·47
Systolic pulmonary artery pressure (mm Hg)	32	32	32	34	30	31	3·77	NS	3·40
Diastolic pulmonary artery pressure (mm Hg)	16	16	16	16	15	15	2·18	NS	1·97
Mean pulmonary artery pressure (mm Hg)	21	21	21	22	20	20	2·42	NS	2·18
Central venous pressure (mm Hg)	6	6	6	6	6	5	1·22	NS	1·09
Cardiac output (l/min)	4·03	5·99	5·92	5·61	5·84	5·70	0·432	<0·001	0·370
Cardiac index (l $min^{-1}m^{-2}$)	2·16	3·22	3·16	3·01	3·13	3·07	0·243	<0·001	0·208
Stroke volume index (ml $beat^{-1}m^{-2}$)	28·6	35·7	35·0	33·7	34·5	33·0	2·86	<0·001	2·45
Systemic vascular resistance index (units/m^{-2})	40·7	28·2	29·3	30·3	26·7	30·1	3·45	<0·001	3·11
Left ventricular stroke work index (gxm/m^2)	29·3	39·2	38·7	35·4	34·8	35·0	4·22	<0·001	3·62

LSD, least significant difference.

after the end of the infusion. The dose titration performed in phase 1 was then repeated.

Haemodynamic data were recorded at − 20 minutes, − 5 minutes and immediately before the dopexamine infusion and every 15 minutes during the dose titration (before the dose was increased). During the long term infusion, data were recorded at 30 minutes and at 1, 2, 3, 4, 8, 12, 20, and 24 hours.

STATISTICAL METHODS AND ANALYSIS

Dose titrations were analysed by two way analysis of variance with the dose and patient as factors. Where there was a significant treatment effect, paired data were compared by the least significant difference method.

A two way analysis of variance was also used to analyse the continuous infusion but with time and the patient as factors.

The two controls and the two dose titrations were compared by a paired *t* test.

All statistical tests were two tailed and a p value of < 0·05 was regarded as significant.

Results

FIRST DOSE TITRATION (PHASE 1)

Data recorded during the initial dose titration were analysed to assesss the short term effect (table 2). During this dose titration all 15 patients received the lowest infusion rate (0·5 μg/kg/min), 12 patients

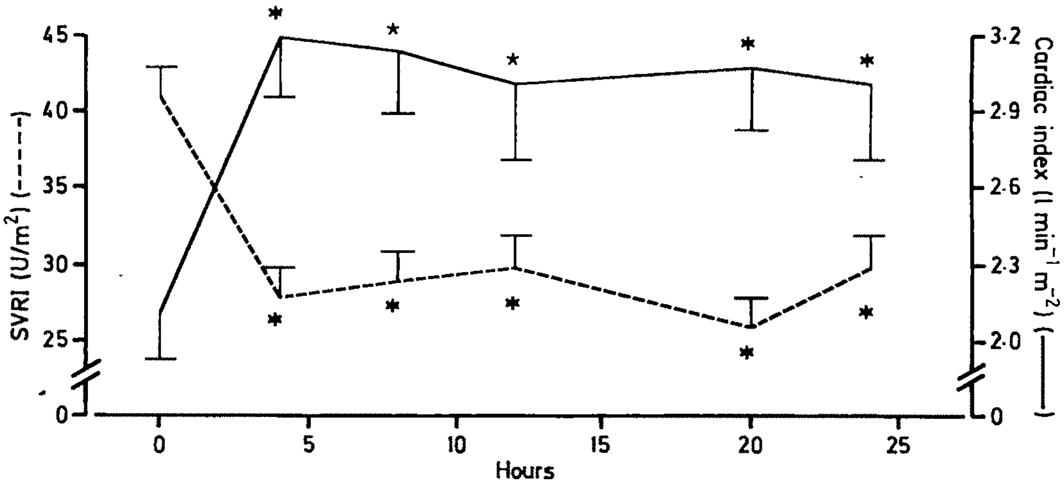

Fig 3 *Effects (mean (SEM)) of dopexamine hydrochloride during the long term infusion on systemic vascular resistance index and cardiac index. *Significantly different from baseline values.*

Table 4 *Haemodynamic data from the second dose titration (phase 3)*

Haemodynamic variable	*Infusion rate (μg/kg/min)* 0	0·5	1·0	*Standard deviation*	*Significance (p)*	*LSD (0·05)*
Heart rate (beat/min)	89	93	95	2·06	<0·001	1·93
Systolic blood pressure (mm Hg)	119	122	126	3·59	<0·01	3·37
Diastolic blood pressure (mm Hg)	76	73	73	3·99	NS	3·75
Mean blood pressure (mm Hg)	90	89	90	3·11	NS	2·92
Systolic pulmonary artery pressure (mm Hg)	30	30	30	1·13	NS	1·06
Diastolic pulmonary artery pressure (mm Hg)	16	15	15	1·16	NS	1·09
Mean pulmonary artery pressure (mm Hg)	20	20	20	1·09	NS	1·02
Central venous pressure (mm Hg)	6	6	5	1·155	NS	1·085
Cardiac output (l/min)	4·26	4·71	5·23	0·347	<0·001	0·326
Cardiac index (l min^{-1}m^{-2})	2·34	2·60	2·88	0·179	<0·001	0·168
Stroke volume index (ml beat^{-1}m^{-2})	26·9	28·6	30·9	2·22	<0·001	2·09
Systemic vascular resistance index (units/m^{-2})	37·7	33·5	31·1	2·58	<0·001	2·43
Left ventricular stroke work index (gm/m^2)	27·5	29·0	31·7	2·67	<0·01	2·51

LSD, least significant difference

received 1·0 μg/kg/min, four patients received 2·0 μg/kg/min, and one patient 4·0 μg/kg/min. So we compared the control values with the first two dose points (0·5 and 1·0 μg/kg/min). This analysis is based on data from 12 patients.

The systemic vascular resistance index was significantly reduced by 13% for 0·5 μg/kg/min and by 25% for 1·0 μg/kg/min (fig 2). Both doses produced significant increases in cardiac index of 15% and 32% respectively. Similarly, stroke index increased significantly by 12% and 23%. Heart rate was not significantly changed at 0·5 μg/kg/min (increase of 2 beats/min). The small increase of 7 beats/min at the 1 μg/kg/min dose was, however, statistically significant. There was no change in diastolic or mean arterial blood pressure, but the systolic blood pressure rose significantly by 4% and 5% respectively. Left ventricular filling pressure was not affected.

LONG TERM INFUSION (PHASE 2)

The dose of dopexamine that produced the best haemodynamic response was chosen for the long term infusion.

One patient was withdrawn after the first dose titration because of chest pain and tachycardia. The infusion was stopped after 3 hours in one patient (technical failure), after four hours in one patient (chest pain), and after 22 hours in one patient (patient's request), and these patients are excluded from the statistical analysis. Data recorded at baseline, 4, 8, 12, 20 and 24 hours were compared (table 3).

A comparison of tables 2 and 3 shows that the differences between baseline values and 1·0 μg/kg/min during the dose titration and those between baseline values and the four hour time point are not the same. Additionally, baseline values in table 2 are slightly different from those in table 3. There are two reasons for this. Firstly the two populations are slightly different; the twelve patients who received the 0·5 and 1·0 μg/kg/min infusion rates are not the same as the eleven for whom data were available for all time points on the 24 hour analysis. Secondly, table 3 includes data from patients who subsequently went on to receive infusion rates higher than 10 μg/kg/min.

Cardiac index, stroke volume index, left ventricular stroke work index, and heart rate were significantly higher than baseline values at all time points and the systemic vascular resistance index was lower (fig 3). Systolic, diastolic, and mean blood pressure response at 4, 8, and 12 hours was significantly different from baseline. Left ventricular filling pressure was not affected.

SECOND DOSE TITRATION (PHASE 3)

During the second dose titration cardiac index (11% and 23%), stroke volume index (6% and 15%) and systolic blood pressure (5%) were significantly higher than baseline for the 0·5 and 1 μg/kg/min doses (table 4). As during the first dose titration the heart rate was not significantly changed at the lower dose but the small increase of 7 beats/min at the higher dose was statistically significant. The systemic vascular resistance index decreased significantly.

Baseline values for cardiac index and heart rate were higher during phase 3 than during phase 1. The responses to the two doses of dopexamine during the two phases were not significantly different (fig 4). This indicates that no tolerance had developed to the effect of dopexamine.

SIDE EFFECTS

Three patients experienced unusual symptoms during the study. In patient 3 angina developed at the 1 μg/kg/min dose; it disappeared when the dose was reduced to 0·5 μg/kg/min. Patient 12 showed increases in heart rate and blood pressure and also

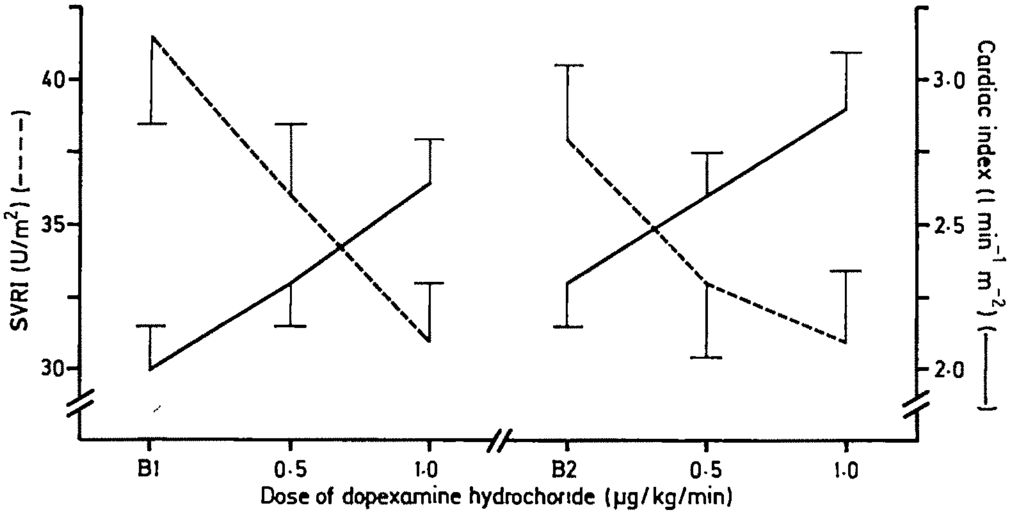

Fig 4 *A comparison of the effect (mean (SEM)) of two dose titrations on systemic vascular resistance index and cardiac index shows no significant differences between the responses to the two doses of dopexamine hydrochloride on the two occasions. B1, baseline value for first dose titration; B2, baseline value for second dose titration.*

developed chest pain at the 0·5 μg/kg/min dose (during dose titration), and patient 5 had angina at the 0·5 μg/kg/min dose (after three hours of the long term infusion). The infusion was terminated in patients 5 and 12.

Discussion

We studied the haemodynamic effects of dopexamine during dose titration in patients with mild to moderate heart failure after myocardial infarction. We also investigated whether any of the effects shown during dose titration could be maintained during a 24 hour period of continued infusion and whether tolerance developed. As this was the first trial of dopexamine in patients with acute myocardial infarction an open study was considered to be safer. The initial dose titration was important because the haemodynamic effect of dopexamine in human volunteers and patients with chronic heart failure would not necessarily be the same in acute heart failure. This is because dopexamine is a potent, competitive inhibitor of the neuronal uptake of catecholamines and the effects might be expected to be more pronounced in patients with myocardial infarction in whom sympathetic tone is high. In fact, the doses used in this study are lower than in studies of dopexamine in patients with chronic heart failure.[18,20] The situation in acute failure after myocardial infarction is, however, complicated and an increased filling pressure in the left ventricle may not always indicate true failure, but only an altered state of compliance of the left ventricular wall. This situation may be entirely different from that of chronic failure in which peripheral resistance is increased and cardiac output reduced. A difference in the number of as well as sensitivity of the β receptors of the heart between patients with heart failure after acute myocardial infarction and those with chronic heart failure could be another reason why our patients responded at lower dose levels.

We found that dopexamine improved haemodynamic function after myocardial infarction. Cardiac output and stroke volume were increased and afterload was reduced. This finding is consistent with the known pharmacology of dopexamine and to a large extent is attributable to considerable vasodilator activity, primarily arterial, reducing systemic vascular resistance.[14,15] During the long term infusion the initial effects were well sustained. Over this period there were slight and apparently spontaneous changes in systemic vascular resistance, blood pressure, and heart rate. This could be explained by an initial high level of circulating catecholamines and high sympathetic tone causing peripheral vasoconstriction. With time the effects become attenuated as the endogenous catecholamine concentrations fell and the reduction in afterload was effected by a reduction in endogenous adrenergic stimulation while the β_2 stimulant effect of the infusion was maintained. The increase in heart rate during the end of the 24 hour infusion may therefore be mediated by the baroreceptor.

Three patients had tachycardia associated with angina. When dopexamine was stopped or reduced both symptoms resolved. Although angina pectoris is a common symptom after acute myocardial infarction, the increase in heart rate preceding the anginal episodes means that the tachycardia is likely to be the precipitating event. Whether the positive inotropic effect of dopexamine is important in this respect is unclear. The increase in heart rate seen in some of our patients could, however, make dopexamine less suitable in patients with remaining ischaemia. A careful dose titration with close monitoring of heart rate and symptoms is therefore recommended in patients with post-infarction failure.

Development of tolerance after treatment with β adrenergic agonists is associated with receptor down regulation. This phenomenon seems to result from both a decrease in the number of as well as a desensitisation of the β receptors.[22–25] Although dopexamine has a weak β_1 effect the reproducibility of the dose response curve at the second dose titration indicates that tolerance did not develop during a 24 hour period. This is further supported by the persistence of the effects seen initially during the long term infusion.

Although cardiac output was low in most of our patients, they were only in mild heart failure. As yet we do not know whether dopexamine can produce useful effects in more advanced heart failure including patients with very high filling pressures. Our patients were investigated in rest only; during exercise the haemodynamic changes caused by dopexamine may be different.

Additional studies are needed to confirm our observations and the possible role of dopexamine in the short term treatment of heart failure.

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Flecainide compared with a combination of digoxin and disopyramide for acute atrial arrhythmias after cardiopulmonary bypass

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SUMMARY Fifty six adult patients were randomised to treatment with flecainide (group 1, n = 29) or a combination of digoxin and disopyramide (group 2, n = 27) for acute atrial fibrillation and flutter after cardiac surgery. Intravenous flecainide was given as a 2 mg/kg bolus over 20 minutes followed by an infusion (0·2 mg/kg per hour) for 12 hours. Group 2 were given digoxin (0·75 mg) intravenously followed two hours later by an intravenous bolus of disopyramide (2 mg/kg) and an infusion (0·4 mg/kg per hour) for 10 hours. Within 12 hours sinus rhythm was restored in 86% of the group 1 (25 patients) and 89% of the group 2 (24 patients). The median time to reversion was significantly shorter in group 1 (80 minutes, range 30–180 minutes) than group 2 (220 minutes, range 138–523 minutes). None of the patients in group 1 and four of the patients in group 2 had transient relapses into atrial fibrillation during the 12 hours of intravenous treatment. There were five late relapses in group 1 and seven in group 2 during subsequent oral treatment. Two group 1 patients and two group 2 patients showed adverse drug effects. Intractable ventricular arrhythmias occurred after five days of oral treatment in one patient (group 1) who had poor left ventricular function, hepatic impairment, and toxic concentrations of drugs at the time of death.

Flecainide was as effective as the combination of digoxin and disopyramide and it acted significantly faster and was associated with fewer relapses. Monitoring of blood concentrations of flecainide is essential in patients with poor left ventricular function and hepatic impairment.

The early postoperative course after open heart surgery is complicated by supraventricular arrhythmias (usually atrial fibrillation or flutter) in 15–90% of patients.[1-3] Although reversion to sinus rhythm may occur promptly without treatment, an appreciable proportion of patients will have persistent arrhythmias associated with a rapid ventricular rate, causing distress, impaired myocardial performance, and symptomatic haemodynamic deterioration.

An earlier study at our hospital showed that intravenous sotalol was as effective as a combination of digoxin and disopyramide in restoring sinus rhythm and that it acted significantly faster.[4] The frequent occurrence of hypotension during the intravenous administration of sotalol and the relatively common anticholinergic side effects of disopyramide prompted further investigation of alternative treatment regimens.

In several recent studies flecainide acetate, a class 1c antiarrhythmic drug, was effective in the treatment of spontaneous and inducible supraventricular arrhythmias.[5-7] In the present study we compared the efficacy and side effects of flecainide given alone with those of a combination of digoxin and disopyramide in patients with acute atrial fibrillation or atrial flutter after cardiac surgery.

Patients and methods

We studied patients who had heart operations from December 1985 to August 1986 and in whom atrial arrhythmias with a ventricular rate > 110 beats/min developed after operation. Criteria for exclusion were a history of glaucoma, urinary retention, severe renal impairment (serum creatinine > 0·24 mmol/l),

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preoperative atrial arrhythmia or atrioventricular block (second or third degree), bifascicular block, left ventricular ejection fraction < 30%, and the administration of any antiarrhythmic drug (including β blockers and digitalis) in the preceding 48 hours.

This was an open parallel group study. If the arrhythmia was present for at least 15 minutes eligible patients were randomly assigned, to one of two groups. The patients in group 1 were given flecainide acetate (Tambocor, Riker Laboratories) (2 mg/kg intravenously over 20 minutes followed by a continuous infusion (in 5% dextrose) of 0·2 mg/kg every hour for 12 hours). Those in group 2 were given an intravenous bolus of digoxin (0·75 mg). If sinus rhythm was restored within two hours intravenous digoxin (0·25 mg twice daily) was continued. If the arrhythmia persisted for more than two hours patients in group 2 were given disopyramide 2 mg/kg intravenously (maximum 150 mg) over 10 minutes followed by an infusion (in 5% dextrose) of 0·4 mg/kg every hour for 10 hours.

The formal comparison of these two treatment regimens ended after the 12 hours of intravenous treatment. The patients in group 1, however, who reverted to sinus rhythm continued to take oral flecainide 100 mg twice a day for the remainder of their hospital stay and for one month after discharge. Similarly, patients who reverted on digoxin alone continued on oral digoxin 0·25 mg/day, and those who reverted on the combination of digoxin and disopyramide continued taking oral digoxin 0·25 mg/day and disopyramide 150 mg four times a day. For both treatment groups, if the arrhythmia persisted after 12 hours of intravenous treatment, further treatment was prescribed by the attending cardiologist.

The electrocardiogram was monitored continuously on a screen and rhythm strips were taken at the time of any rhythm changes. Blood pressure was measured every two minutes for 10 minutes, then every 15 minutes for one hour, and then hourly for 12 hours.

Twelve lead electrocardiograms were recorded during the arrhythmia and within twelve hours of its termination. In those treated with flecainide, blood was collected for measurement of plasma concentrations one hour and 12 hours after start of treatment. Blood for disopyramide assays was not routinely collected in group 2 because this regimen had been shown to produce therapeutic concentrations in similar patients.[8]

STATISTICAL ANALYSIS

The times to reversion of the arrhythmia are given as the median and interquartile range. The distribution of results in group 1 was highly skewed and so we used the non-parametric Wilcoxon rank sum test to test for the significance of differences in reversion times. Results were otherwise expressed as (mean (SD)). We used Student's *t* test to test for significance of difference in age between the two treatment groups. The χ^2 test was used to analyse the differences in reversion rates and relapse rates between both groups.

Results

Of the 58 eligible patients, 30 were randomly assigned to group 1 and 28 to group 2. In one of the group 2 patients with atrial flutter 1:1 atrioventricular conduction developed before the start of antiarrhythmic treatment. The patient's rhythm rapidly degenerated into ventricular fibrillation necessitating urgent cardioversion with the re-establishment of sinus rhythm. This patient was excluded from the analysis.

Another patient from group 1 was treated with intravenous verapamil 30 minutes before the flecainide bolus and reverted to sinus rhythm after 3·5 hours. This patient was also excluded from the analysis because another antiarrhythmic was used within 48 hours of the study.

The table shows the clinical details of the remaining 56 patients. There were no significant differences between the two groups in age, sex ratio, time to onset of arrhythmia, and ventricular rates before treatment. In 25 of the 29 patients in group 1 sinus rhythm was restored during the 12 hours of intravenous flecainide treatment (figure). Reversion to sinus rhythm occurred 30–180 minutes (median 80 minutes) after the start of the intravenous flecainide

Table *Patient details*

Data	*Group 1*	*Group 2*
Number	29	27
Male:female	24:5	20·7
Age (yr)	61·9 (7·3)	61·8 (12·7)
Time to onset of arrhythmia* (hrs)	67·6 (41·4)	62·9 (29·4)
AF:AFL	25:4	24·3
Pretreatment ventricular rate (beats/min)	152 (35·6)	168 (44·4)
Pre-reversion ventricular rate (beats/min)	142 (33·5)	154 (28·1)
No taking β blockers preoperatively	20	21
No undergoing CABG†	26	23
No with preoperative ejection fraction < 0·5‡	5	4

*Measured from the start of cardiopulmonary bypass to the onset of arrhythmia.

AF, atrial fibrillation; AFL, atrial flutter.

†Group 1: two patients had coronary artery bypass grafting (CABG) plus aortic valve replacement, one had repeat mitral valve replacement, and one had repair of an atrial septal defect. Group 2: three patients had aortic valve replacement and one had a mitral valvotomy.

‡Measured at left ventriculography.

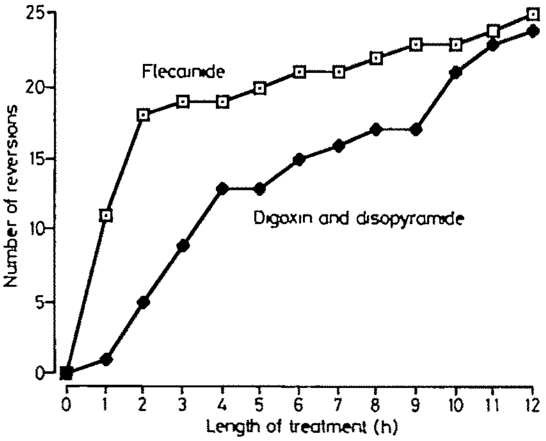

Figure *Time course of reversion to sinus rhythm of patients treated with flecainide (group 1) and with a combination of digoxin and disopyramide (group 2).*

bolus; in 11 patients the rhythm reverted within an hour. Plasma concentrations of flecainide ranged from 160 to 450 ng/ml (mean 306 ng/ml) at one hour and from 280 to 657 ng/ml (mean 434 ng/ml) at 12 hours. In four patients sinus rhythm did not return during the 12 hours of intravenous flecainide treatment. In two of these, both with atrial fibrillation and flutter, atrial flutter persisted after full intravenous dose of flecainide had been given. One reverted to sinus rhythm six hours after starting oral flecainide and the other returned to sinus rhythm after 82 hours on digoxin and disopyramide after oral flecainide had been stopped. A third patient remained in atrial fibrillation despite the full flecainide infusion, and this arrhythmia persisted for the next five days despite treatment with oral digoxin, flecainide, and, later, quinidine. On day 5 electrical cardioversion to sinus rhythm was successful. The fourth patient received the full dose of intravenous flecainide and remained in atrial fibrillation despite continued oral flecainide (initially at 200 mg/day and later 300 mg/day).

In group 2, 24 out of 27 patients reverted to sinus rhythm within 12 hours (figure). The time to reversion after the bolus of digoxin ranged from 138 to 523 minutes (median 220 minutes). The time to reversion was significantly longer than that in group 1 ($p < 0\cdot001$). Five patients reverted with digoxin alone at a median of 105 minutes after the bolus and 19 required the combination of digoxin and disopyramide (reverting at a median of 315 minutes after the start of treatment). The three patients in group 2 with persistent arrhythmias at 12 hours returned to sinus rhythm after 24, 29, and 29 hours respectively of continued oral digoxin and disopyramide.

No patients in group 1 relapsed during the 12 hours of intravenous flecainide; however, five patients relapsed 5–91 hours after the flecainide infusion. In two of these the initial oral flecainide dose had been delayed by nine hours. All five patients reverted to stable sinus rhythm 3–59 hours after relapse, two were continuing to take flecainide 200 mg/day, one flecainide and digoxin, one flecainide 300 mg/day, and one on digoxin and quinidine.

Two patients who reverted with digoxin alone relapsed 10 minutes and 30 minutes later. They were given intravenous disopyramide and in both of them sinus rhythm returned within 60 minutes. Two patients who responded initially to digoxin and disopyramide relapsed during the disopyramide infusion at two hours and 10 hours. On continued intravenous disopyramide they reverted to sinus rhythm at 10 minutes and five hours respectively. Seven patients who reverted during treatment with digoxin and disopyramide relapsed (after the disopyramide infusion) 6–114 hours after the initial reversion. Three continued on digoxin and disopyramide and reverted to sinus rhythm 10 hours, 13 hours, and 70 hours later. Three were treated with digoxin and quinidine and reverted at two, 15, and 19 hours; and another reverted at 12 hours with digoxin, quinidine, and atrial overdrive pacing for persistent atrial flutter.

SIDE EFFECTS

Most patients did not show any untoward changes in vital signs after operation. In one patient blood pressure fell significantly from 120 mm Hg to 90 mm Hg (systolic) immediately after intravenous flecainide. In this case the rhythm was atrial fibrillation with a ventricular rate of 160/min. After the administration of 100 ml of colloid (Haemacel) the blood pressure returned promptly to its previous value without further sequelae.

Another patient, a 68 year old man with congestive heart failure, underwent repeat operation for a leaking mitral valve prosthesis and single coronary artery graft, and atrial fibrillation developed postoperatively. The preoperative left ventricular ejection fraction was 0·34. Serum concentrations of hepatic transaminases were raised before operation. The arrhythmia persisted despite treatment with flecainide and the dose was increased to 300 mg/day. The QRS complex progressively widened to 0·17 seconds over the next three days without reversion to sinus rhythm. Then treatment with digoxin (0·25 mg/day) then started. Within 36 hours the patient became dyspnoeic and developed sustained ventricular tachycardia (QRS width 0 24 seconds), which was refractory to repeated cardioversion and several antiarrhythmic agents. Cardiopulmonary resuscitation was unsuccessful and at death the plasma concentration of flecainide was 2000 ng/ml (4·0 μmol/l).

No adverse effects were noted during the initial 12 hours of treatment in group 2, however, in two patients oral disopyramide (600 mg/day) was stopped because of acute urinary retention.

Discussion

Several recent studies have shown that flecainide acetate is an effective treatment for converting atrial fibrillation and atrioventricular reentrant tachycardias to sinus rhythm.[5-7] The clinical nature and duration of the arrhythmia in these studies varied. The arrhythmias studied were: tachycardia induced by programmed stimulation,[5] paroxysmal tachycardia sustained for up to 24 hours,[9] tachycardia of < 12 hours' duration,[10] atrial fibrillation of "recent" onset (within three months),[11] and atrial fibrillation that had present for up to 140 days.[12] Despite these different clinical features of the target arrhythmia, flecainide acetate was a very effective treatment, both intravenously and orally, particularly for arrhythmias of recent onset. Reversion of atrial fibrillation (79–90%) and atrioventricular re-entrant tachycardias (89%) was successful, but the results of treating recent onset atrial flutter (20–40%) were disappointing.[6 9 10]

Few studies have compared the efficacy of flecainide with that of other antiarrhythmic drugs in supraventricular arrhythmias. The study by Borgeat *et al*, comparing flecainide given intravenously and by mouth with quinidine given by mouth, showed that flecainide was at least as effective as quinidine (86% *v* 80%) in terminating atrial fibrillation of less than 10 days' duration.[12] For suppression of recurrent paroxysmal atrial fibrillation prophylaxis with flecainide in combination with digoxin was more effective than a combination of quinidine and digoxin and a digoxin-only group.[13]

We found that flecainide was as effective as a combination of digoxin and disopyramide in reverting acute onset arrhythmia within 12 hours of start of treatment (86% *v* 89% respectively). The time to reversion to sinus rhythm was significantly shorter in the flecainide group, with 72% of patients reverting within two hours of treatment compared with only 21% of patients receiving the standard treatment. The median time to reversion on flecainide was almost one third that of the combination of digoxin and disopyramide (80 min *v* 220 min, $p < 0{\cdot}001$). Furthermore, during the observation period of intravenous and continued oral treatment there were far fewer relapses in the flecainide group.

The choice of flecainide as first line treatment for symptomatic atrial arrhythmias after open heart surgery follows from previous studies at our hospital of the efficacy of disopyramide and sotalol in similar patients.[1 4] Unfortunately side effects often limited the continued use of disopyramide and sotalol and prompted this trial of an alternative treatment. Several studies have evaluated the prophylactic use of low dose β blockers in the immediate postoperative period and have shown a significant reduction in the incidence of supraventricular arrhythmias.[2 3 14] The frequency of arrhythmia in the control groups in these studies (16–94%) has, in most cases, been higher than the 25% previously found at our hospital.

There is an understandable reluctance to treat all patients in order to prevent an arrhythmia in a limited number most of whom will respond promptly to specific antiarrhythmic treatment. As a result of the rapid restoration of sinus rhythm with this flecainide treatment, it has now been adopted at our hospital as the usual treatment for postoperative atrial arrhythmias.

Side effects were equally common in both groups, however, a lethal arrhythmia developed while one patient was being treated with flecainide (300 mg/day). The risk in this patient was increased by poor left ventricular function and repeat operation for mitral valve and coronary artery disease. In such cases the incidence of arrhythmogenic effects of antiarrhythmic agents approaches 20% and may be associated with toxic plasma concentrations.[15] Frequent monitoring of plasma concentrations with cautious increases in dose (not more often than every four days) is important in patients with heart failure, who have a prolonged elimination half life.[16 17]

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Effect of changes in heart rate on pressure half time in normally functioning mitral valve prostheses

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SUMMARY To test the validity of a relation between the pressure half time and the diastolic time interval, previously shown in a pulse duplication system, eight patients with prosthetic mitral valves and permanent pacemaker systems were studied. Recordings were made from the apex by continuous wave or pulsed Doppler echocardiography at heart rates between 75 and 150 beats/min. The pressure half time was found to be closely correlated with the diastolic time interval although there was individual variation and in three prostheses the pressure half time attained a plateau when the diastolic time interval was more than 300 ms.

It is likely that the orifice area is the main controller of pressure half time where there is stenosis of the prosthesis, but that other factors such as ventricular or atrial compliance and the diastolic time interval may modify or obscure the effect of orifice area in normally functioning prosthetic valves.

The pressure half time is a measure of the rate of depressurisation of the left atrium and it is thought to be a comparatively flow independent indicator of orifice area in native mitral stenosis.[1-3] There are, however, inconsistencies where pressure half time is considered in normally functioning mitral prostheses. The pressure half time correlates poorly with annulus diameter and may vary widely for one valve type between studies.[4 5] There may be little difference in pressure half time in valves of widely different design.[6] It is therefore likely that where the area of the orifice is comparatively large, other factors such as ventricular or atrial compliance and diastolic filling time may have a disproportionate effect on pressure half time.[7 8] Most studies, however, that have attempted to establish normal ranges for prosthetic function did not report information about flow or ventricular function.[4 6 9]

We showed in a pulse duplicator system with a regular cycle rate and stroke volume that pressure half time is independent of stroke volume but directly related to the diastolic time interval.[7] In the present study we used patients with permanent pacemaker generators as a model with constant cycle length to test the effect of changing diastolic length on pressure half time.

Patients and methods

PATIENTS AND PROCEDURE

All nine patients on the King's College Hospital database with both mitral prostheses and permanent implanted multiprogrammable pacemaker generators were recruited. In one, differences in the timing of atrial activity made the shape of the Doppler waveform too variable for analysis. The table shows details of the remaining eight patients. All had VVI systems. No patient had symptoms or signs of either heart failure or prosthetic dysfunction although one (case 2) had a dilated, hypokinetic left ventricle on echocardiography. Imaging and Doppler echocardiography showed normal cusp or occluder motion in all patients and no appreciable regurgitation.

The procedure was explained and the patient asked to lie semi-recumbent in the left lateral position. A 1·9 MHz continuous wave transducer was used except in one patient with a bioprosthesis in whom pulsed Doppler with a duplex 2·5 MHz transducer with the sample volume at the level of the stent tips gave better signals. The probes were placed in the apical position and oriented with the forward flow by means of colour flow mapping. An assistant increased the pacemaker rate by 10 beats/min up to the highest programmable rate and then reduced it below the normally set rate until the patient's spontaneous rhythm supervened. After a delay of 20 seconds at each increment at least 20 Doppler signals were recorded onto thermal paper run at 100 ms/s.

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Table *Demographic data in patients with permanent pacemaker generators and mitral prostheses*

Case	*Valve type*	*Pacemaker type*	*LV function*	*Rhythm before pacing*
1	B–S	Telectronics Optima	Normal	CHB
2	B–S	Telectronics Optima	Poor	CHB
3	S–E	Telectronics Optima	Normal	Slow AF
4	C–E	Telectronics Optima	Normal	Slow AF
5	C–E	Biotronic Neos	Normal	Sinus pauses
6	C–E	Cordis Stanicor Gamma	Normal	Slow AF
7	S–E	Siemens 748T Dialog	Normal	Sinus pauses
8	S–E	Telectronics Optima	Normal	CHB

AF, atrial fibrillation; B–S, Björk-Shiley; C–E, Carpentier-Edwards; CHB, complete heart block; LV, left ventricular; S–E, Starr-Edwards.

DATA ANALYSIS AND STATISTICAL ANALYSIS

Pressure half time was taken as the time for peak left ventricular inflow velocity to fall to $0\cdot7 \times$ peak.[1] Many of the recordings had nonlinear deceleration slopes so we made measurements directly from the outline of the envelope rather than attempting to rule lines tangential to the waveform. Pressure half time was measured over 5–8 complexes at each cycle length and the mean and standard deviation were calculated. The diastolic time interval was measured from the start of the opening artefact to the midpoint of the closing artefact on each complex and the mean value was taken. Regression lines were drawn with standard commercially available computer software (Amstat1).

Results

RELATION BETWEEN DIASTOLIC INTERVAL AND CYCLE LENGTH

The diastolic time interval was directly related to cycle length ($r = 0\cdot97$, $y = 0\cdot80x - 222\cdot64$, 95% confidence interval for the slope $0\cdot76$ to $0\cdot84$ and for the intercept $188\cdot75$ to $256\cdot53$ ($p < 0\cdot00001$) (fig 1).

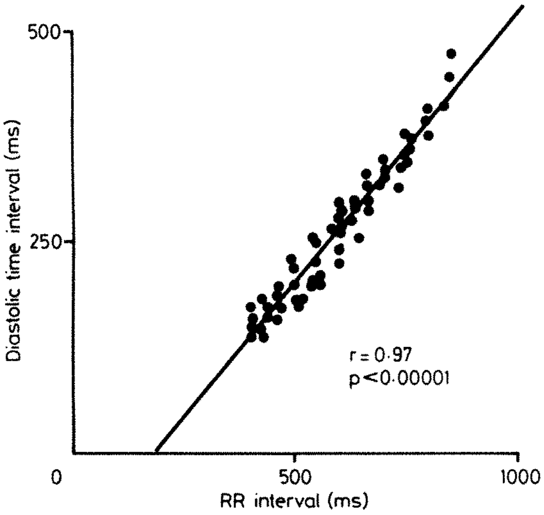


Fig 1 *Diastolic time interval plotted against RR interval. The regression line is shown in bold.*

RELATION BETWEEN PRESSURE HALF TIME AND DIASTOLIC TIME INTERVAL

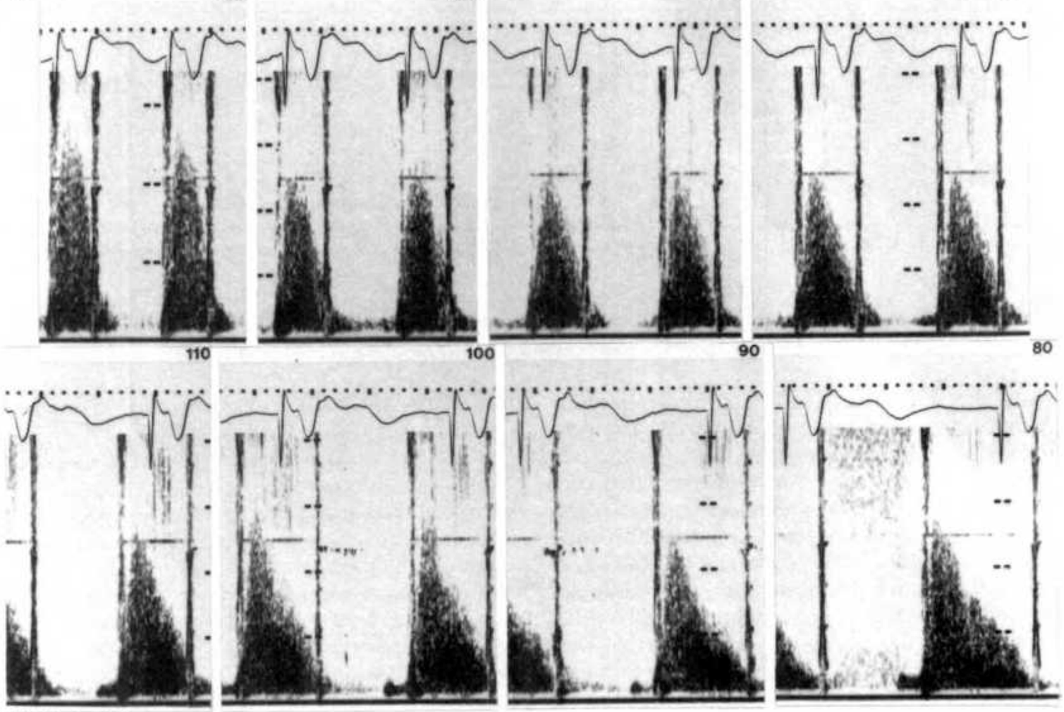
Spectral recordings were generally satisfactory except in some patients at high rates when dense valve artefacts made measurement of pressure half time difficult. These traces were not measured. Examples of spectral recordings are given in fig 2a and b. In patient 3, the waveform had a fast deceleration phase and a subsequent slower phase which was seen only at lower heart rates. In the other patients, the basic configuration did not change but the waveform became wider at lower rates.

The pressure half time was directly related to the diastolic time interval ($r = 0\cdot81$, $y = 8\cdot77 + 0\cdot28x$, 95% confidence interval for intercept $-5\cdot71$ to $23\cdot25$ and slope $0\cdot23$ to $0\cdot33$, $p < 0\cdot00001$) (fig 3). In most patients the relation between the pressure half time and the diastolic time interval was linear, although in two patients (cases 4 and 6) with a bioprosthesis and one with a Starr-Edwards prosthesis (case 7), it was curvilinear (fig 4). The slope of the relation was not dependent on valve type.

Discussion

In native mitral stenosis the pressure half time correlates well with the orifice area assessed by the Gorlin formula at simultaneous catheterisation.[10] The same assumption underlies the universal use of pressure half time in the numerous studies attempting to define normal ranges for prosthetic mitral function.[4–6 9 11 12] Some[6] have even estimated orifice area from pressure half time by an empirical formula (220/pressure half time) derived specifically for native stenosis that has never been validated adequately for prostheses.[1] In fact, it has long been known from echocardiographic studies that the diastolic filling rate is dependent on left ventricular function as well as resistance to flow offered by the mitral valve.[13 14] Thomas and Weyman[8] have derived an expression

(a) Patient 3



(b) Patient 4

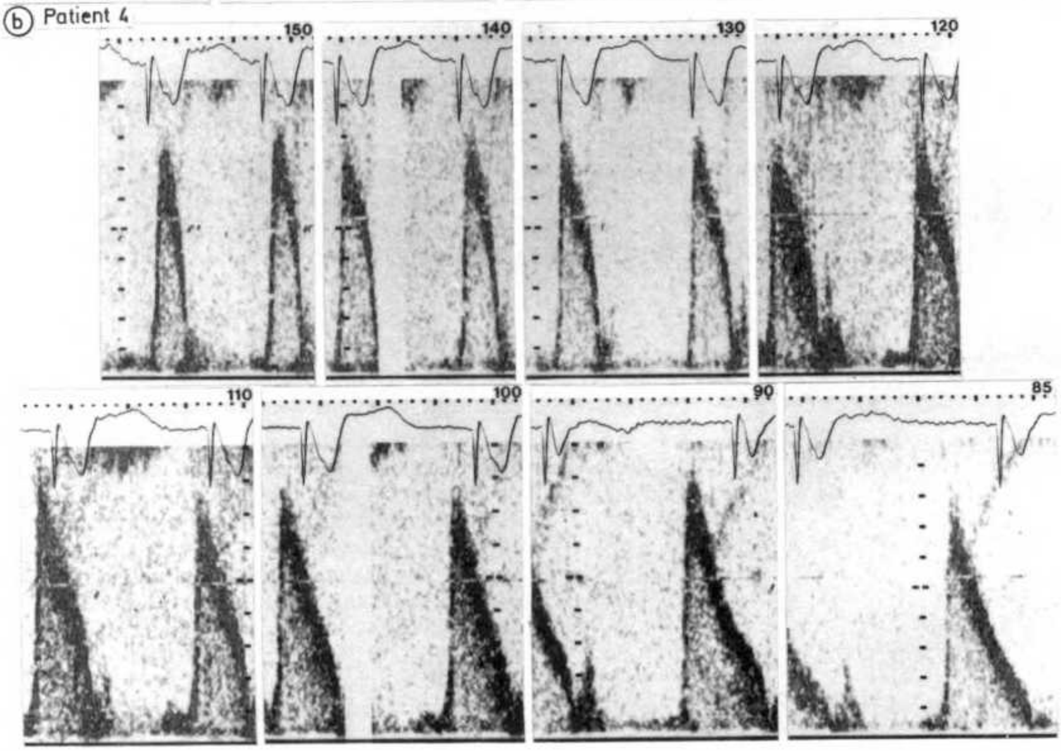


Fig 2 *Two sets of left ventricular inflow recordings. (a) Continuous wave recordings from patient 3 who had a Starr-Edwards prosthetis and (b) pulsed Doppler recordings from patient 4 who had a Carpentier-Edwards prosthesis.*

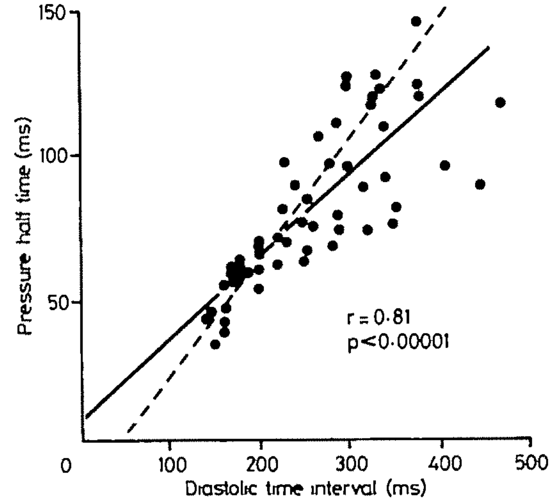


Fig 3 *Pressure half-time plotted against diastolic time interval for all eight prostheses. The regression line from this pooled study is shown as a bold line. That from an experimental circuit is shown as a dotted line.*

for pressure half time based on hydrodynamic theory which can be generalised to:

Pressure half time proportional to $(C.\sqrt{\Delta p})/MVA$

C is combined atrial and ventricular compliance, Δp is the pressure difference between atrium and ventricle at the start of diastole, and MVA is mitral orifice area. These three factors are likely to interact to a degree that varies both with physiological and pathological state. The orifice area may be the main determinant of the pressure half time where there is a prosthetic stenosis, but in normally functioning prostheses its effect may be modified or obscured by the other factors. Thus Panidis *et al* found no difference in the pressure half time between normally functioning Starr-Edwards, Björk-Shiley, and biological prostheses in the mitral position[6] although these valves have widely different behaviour in experimental circuits.[15] The variability in the pressure half time between studies of one prosthesis may partly reflect statistical sampling or differences in technique, but it seems probable that differences in flow and ventricular function must also contribute. The mean pressure half time for Carpentier-Edwards prostheses was 90 ms in a series of 38 reported by Gibbs *et al*,[5] 128 ms in a series reported by Hatle and Angelsen,[16] and 136 ms in 29 cases reported by Ryan *et al*[4] (which however included some Hancock prostheses).

Similarly the effect of rate on atrial or ventricular compliance, atrial pressure, and orifice area is likely to vary with valve type and the presence of ventricular dysfunction. Thus although the relation between pressure half time and diastolic interval in this study was similar to that previously shown in an experimental circuit,[7] there was increased scatter at comparatively long cycle lengths, and in some prostheses the pressure half time reached a plateau when

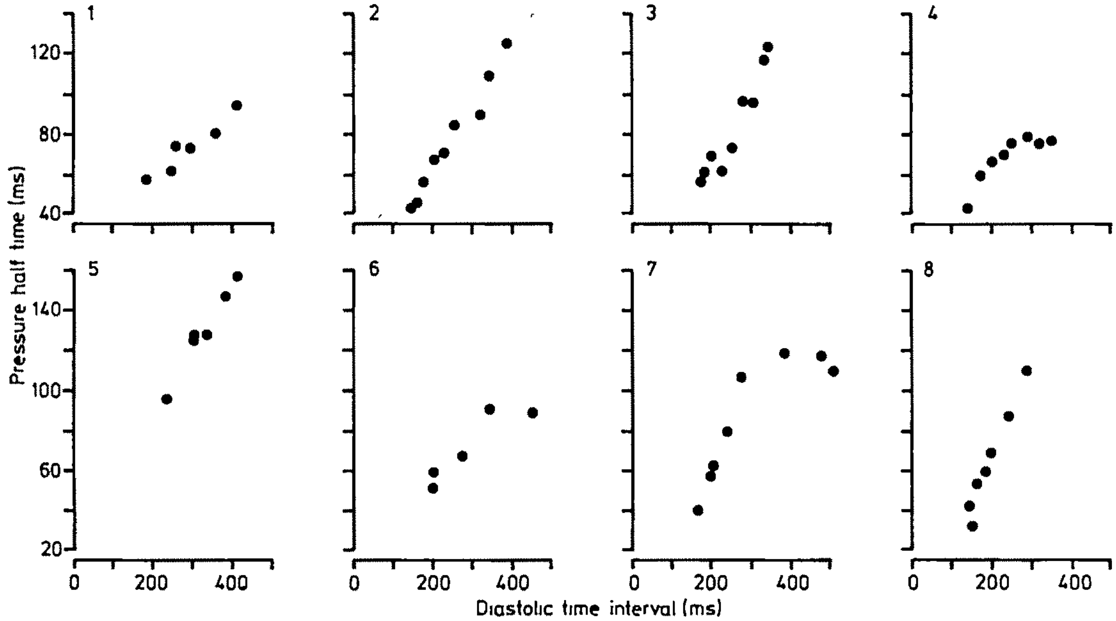


Fig 4 *Pressure half time plotted against diastolic time interval for prostheses in eight patients.*

the diastolic interval was > 300 ms.[7] The relation was not tested at cycle rates below 75 beats/min. The effect of diastolic length may be different in a patient in atrial fibrillation rather than paced rhythm, although when Libanoff and Rodbard used cardiac catheterisation to study patients with mitral stenosis, the pressure half time varied from 110 ms to 170 ms over cycle lengths from 500 ms to 1000 ms.[3]

Pressure half time may be less useful as a measure of orifice area in normally functioning prostheses than has previously been assumed. This is because it may be controlled partly by atrial or ventricular factors and varies with diastolic time interval. This study suggests that if the pressure half time of different valves is compared, cardiac cycles with a diastolic time interval of ⩾300 ms should be chosen.

Dr J B Chambers holds a British Heart Foundation Junior Fellowship.

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Further observations on the effect of balloon size on the short term and intermediate term results of balloon dilatation of the pulmonary valve

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SUMMARY The relation between the size of the balloon used for dilatation of the pulmonary valve and the extent of relief of pulmonary stenosis both immediately after and at intermediate term follow up was studied. Sixty four balloon dilatation procedures in 56 patients were divided into group 1—12 in which the ratio of the diameter of the balloon to that of the pulmonary annulus was ⩽ 1·0—and group 2—52 in which the ratio was > 1·0. Both groups had similar mean (SD) pressure drops across the pulmonary valve before dilatation. Immediately after dilatation there was a significant reduction in the pulmonary valve gradient in both group 1 (84·3 (39·2) *v* 43·6 (26·8) mm Hg) and group 2 (92·8 (42·1) *v* 22·4 (13·6) mm Hg). On intermediate term follow up (6–34 months), residual pulmonary valve gradients were significantly lower in group 2 (20·8 (18·5) mm Hg) than in group 1 (75·0 (49·4) mm Hg), suggesting that restenosis was more common after dilatation with small balloons. These data suggest that although the immediate results with either small or large balloons are good, balloons that are larger than the pulmonary valve annulus produce more sustained relief of pulmonary stenosis. Further analysis within the group treated with larger balloons showed that the subgroup with a balloon/annulus ratio of 1·01—1·2 had more recurrences of stenosis (need for repeat balloon dilatation and larger number of patients with residual pulmonary valve gradients > 30 mm Hg) than subgroups with balloon/annulus ratios for diameters of 1·21—1·41, > 1·41, and > 1·5, in which there were no recurrences. Balloons that were > 1·5 times the size of the pulmonary valve annulus had no additional advantage over the other subgroups, namely, 1·21—1·4 and > 1·41.

These results and reports of damage to the right ventricular outflow tract by oversized (> 1·5) balloons indicate that balloons that give a balloon/annulus ratio of 1·2—1·5 are the best for dilatation of the pulmonary valve.

In a previous study I reported on the relation between the size of the balloon used for balloon dilatation of the pulmonary valve and the degree of relief of pulmonary stenosis and I concluded that although the immediate results of dilatation are similar with both small and large balloons, balloons that are larger than the pulmonary valve annulus seem to produce more sustained relief of pulmonary stenosis on follow up.[1] Therefore, I recommended balloons that were larger than the pulmonary valve annulus for balloon dilatation of the pulmonary valve. Radtke *et al* reported similar relation between ballon size and the immediate results of dilatation.[2] In view of the damage to the right ventricular outflow tract when balloons larger than 1·5 times the size of the pulmonary valve annulus were used,[3] a balloon diameter to annulus diameter ratio of 1·2–1·4 was recommended.[1 2] This was an arbitrary recommendation without specific supporting data. I attempted to break down the group treated with large balloons into subgroups with various balloon/annulus ratios[1] but I did not have sufficient cases in each subgroup to reach valid conclusions. In the present paper I present an evaluation of the effect of balloon size on balloon dilatation of the pulmonary valve in a much larger number of patients and examine what ratio of balloon size to pulmonary valve annulus is most

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apropriate for balloon dilatation in terms of the immediate and intermediate term follow up results.

Patients and methods

During a 50 month period ending in December 1987, 56 infants and children, aged seven days to 20 years (median six years) underwent 64 procedures for balloon dilatation of the pulmonary valve to relieve moderate to severe pulmonary valve stenosis. We obtained informed consent from the parents of each patient. The data obtained and the technique of percutaneous balloon dilatation of the pulmonary valve have been described in detail in earlier papers[4-6] and they are similar to the technique used by others.[7 8] Two balloons were used simultaneously for dilatation in twelve patients in whom the annular diameter was > 20 mm. Initially, we did not use balloons that were larger than the pulmonary valve annulus;[4] later we did.[1] The size of the pulmonary valve annulus was measured from a frame of the lateral projection of the cineangiogram obtained before balloon dilatation and corrected for magnification.[1] I used the balloon size listed by the manufacturer to calculate the balloon/annulus ratio.[1] When two balloons were used simultaneously, the total balloon diameter was calculated according to the formula:

$$\frac{D_1 + D_2 + \pi\left(\frac{D_1}{2} + \frac{D_2}{2}\right)}{\pi}$$

where D_1 and D_2 are the diameters of the balloons used.

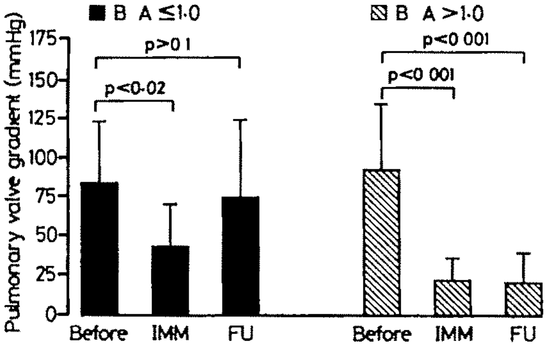

Fig 1 *The peak pressure gradient across the pulmonary valve fell immediately (IMM) after balloon dilatation in both group 1 with small balloons (p < 0·02) and group 2 with large balloons (p < 0 001). On intermediate term follow up (FU), the gradient had risen towards pre-dilatation values (p > 0·1) in group 1 patients (treated with balloons that were smaller than the pulmonary valve annulus) while in group 2 (balloons larger than the pulmonary valve annulus) the gradients remained low.*

Balloon dilatation procedures were divided into two groups, based on the ratio between the balloon size and the size of the pulmonary valve annulus: group 1 with ratio of ⩽ 1·0 and group 2 with ratio of > 1·0. Group 2 was further subdivided into 2a, ratio of 1·01 to 1·2; 2b, 1·21 to 1·4; 2c, > 1·41; and 2d, > 1·5.

Follow up catheterisation was performed in 36 of 56 patients or 39 of the 64 dilatation procedures six to 34 months (mean 10·6 (SD) (6·7) months) after balloon dilatation. The cardiac index (mean (SD)) was obtained by a thermodilution technique in 33 patients and by the Fick method in the remaining patients. There was no difference (p > 0·1) between the cardiac index before dilatation (3·18 (0·84) $l/min/m^2$) and that measured immediately after dilatation (3·16 (0·68) $l/min/m^2$) or at follow up (3·51 (0·8) $l/min/m^2$).

I used a two tailed Student's *t* test to compare data between groups and data obtained before and after dilatation. The Bonferroni correction[9] was applied when multiple comparisons were made. Frequency distributions were compared by the χ^2 test. The level of statistical significance was set at p < 0·05.

Results

There was a total of 64 balloon dilatation procedures in 56 patients; intermediate term follow up was available in 36 patients. In group 1, (12 dilatations), the mean (SD) balloon/annulus ratio was 0·89 (0·08) (range, 0·76–1·0); in group 2 (56 dilatations) the ratio was 1·31 (0·19) (range, 1·01–1·8). The peak systolic pressure gradients across the pulmonary valve before

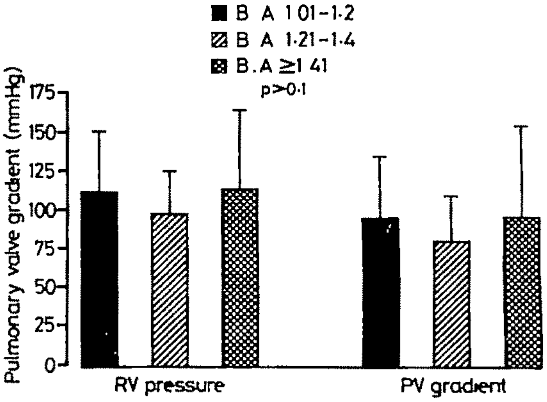

Fig 2 *Right ventricular (RV) peak systolic pressures and pulmonary valve (PV) gradients in all three group 2 subgroups were similar (p > 0·1) suggesting that in all the three groups there was a similar degree of pulmonary valve obstruction.*

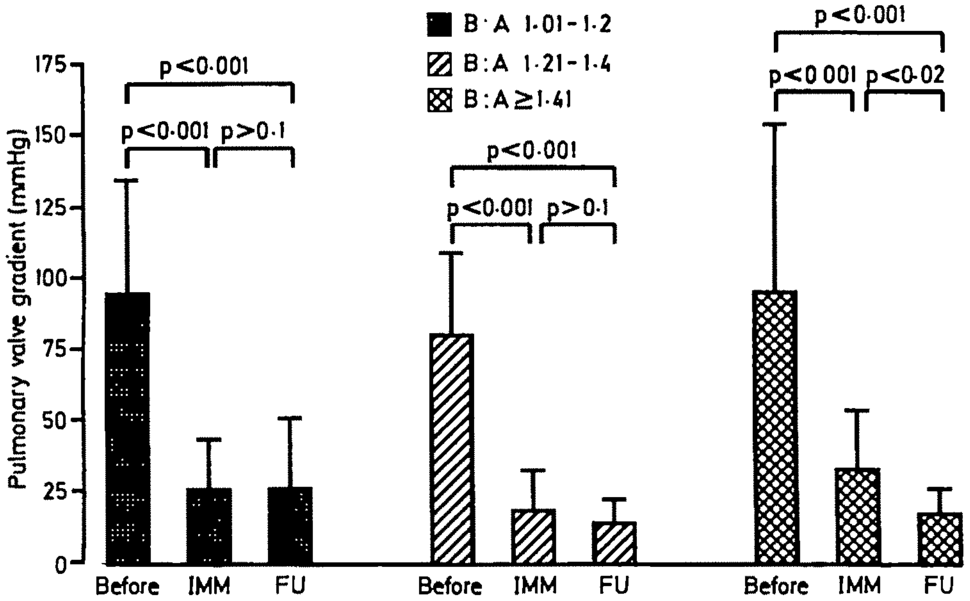

Fig 3 *Peak systolic pressure gradients across the pulmonary valve fell (p < 0·001) immediately (IMM) after balloon dilatation in all three subgroups. On intermediate term follow up (FU), there was either no further change (p > 1·01) (in subgroups with a balloon/annulus ratio of 1·01—1·2 and 1·21—1·4) or a further fall (p < 0 02) (in the subgroup with balloon anulus ratio of > 1·41).*

dilatation were similar in both groups (84·3 (39·2) *v* 29·8 (42·1) mm Hg, p > 0·1).

Immediately after balloon dilatation the pulmonary valve gradient was significantly reduced in both group 1 (84·3 (39·2) *v* (43·6 (26·8) mm Hg, p < 0·02) and group 2 (92·8 (42·1) *v* 22·4 (13·6) mm Hg, p < 0·001) (fig 1). However, the residual pulmonary valve gradients in group 2 with large balloons (22·4 (13·6) mm Hg) were lower (p < 0·01) than those in group 1 with small balloons (43·6 (26·8) mm Hg).

On intermediate term follow up at 6–34 months, the pulmonary valve gradient (75·0 (49·4) mm Hg) in group 1 had risen towards pre-dilatation values (84·3 (39·2)) and was not significantly different from such values (p > 0·1) (fig 1). In group 2 with large balloons the pulmonary valve gradient remained low (20·8 (18·5) mm Hg) and was not significantly different (p > 0·1) from the gradient measured immediately after balloon dilatation. At follow up the right ventricular pressures (97 7 (50·6) *v* 45·5 (17·2) mm Hg, p < 0·02) and pulmonary valve gradients (75·0 (49·4) *v* 20·8 (8·5) mm Hg, p < 0·01) were higher in group 1 than those in group 2 at the follow up. Four of the group 1 patients and one group 2 patient needed repeat balloon dilatation at follow up (p < 0·005). There was Doppler echocardiographic evidence of mild pulmonary insufficiency in 33 of 36 group 2 patients and in three of seven group 1 patients (p < 0·005). No other important complications were seen in either group.

Having confirmed that larger balloon/annulus ratios are associated with sustained relief of pulmonary valve obstruction on follow up, I further subdivided group 2 into group 2a (balloon/annulus ratio, 1·01 to 1·2, 20 patients), group 2b (balloon/annulus ratio, 1·21 to 1·4, 15 patients), and group 2c (balloon/annulus ratio > 1·41, 17 patients). The right ventricular peak systolic pressures and pulmonary valvar gradients were similar (p > 0·1) in those three subgroups (fig 2) although there were minor differences. Reduction of pulmonary valvar gradients immediately after and on intermediate term follow up was seen in all three groups (fig 3). In group 2c (with the largest balloon/annulus ratio (> 1·41) there was a further fall (p < 0·02) in the pulmonary valvar gradients at follow up (18·4 (8·1) mm Hg) when compared to the value measured immediately after dilatation (33·8 (20·1) mm Hg). This may be related to the slightly higher residual pulmonary valvar gradients immediately after dilatation in this subgroup. When the number of patients with residual gradients > 30 mm Hg or the number of patients requiring repeat balloon dilatation were compared (table), group 2a with balloon/annulus ratio of 1·01–1·20 had residual pulmonary valve obstruction while group 2b (ratio 1·21–1·4) and group 2c (ratio > 1·41)

Table *Frequency of repeat balloon and dilatation significant residual gradients in various subgroups*

	Number of patients needing repeat dilatation	*Number of patients with pulmonary valve gradient > 30 mm Hg*
Group 1 (n = 7)	4	6
Group 2a (n = 13)	1	2
Group 2b (n = 9)	0	0
Group 2c (n = 9)	0	0

n = number of patients with intermediate term follow up catheterisation.

had none ($p < 0{\cdot}005$). Group 1 with balloon/annulus ratio < 1·0 had the worst results (table).

Finally, the results of balloon dilatation of patients with balloon/annulus ratios > 1·5 (group 2d, nine patients) were examined (because balloons as large as these are reported to damage the right ventricular outflow tract[3] and were compared with group 2b (balloon/annulus ratio, 1·21–1·4) to see whether there is any advantage in using these oversized balloons (fig 4). The right ventricular systolic pressures (98·0 (27·1) *v* 99·0 (36·9) mm Hg, $p > 0{\cdot}1$) and pulmonary valvar gradients (80·7 (28·6) *v* 82·1 (37·4) mm Hg, $p > 0{\cdot}1$) were similar in both groups. Residual pulmonary valvar gradients immediately after dilatation (19·2 (13·3) *v* 27·8 (13·3), $p > 0{\cdot}1$) and on follow up (14·9 (7·7) *v* 14·0 (5·6), $p > 0{\cdot}1$) were also similar. No patients needed repeat balloon dilatation in either group nor was there any patient with residual pulmonary valve gradient > 30 mm Hg. There was no angiographic evidence of asymptomatic pulmonary arterial tears in either group.

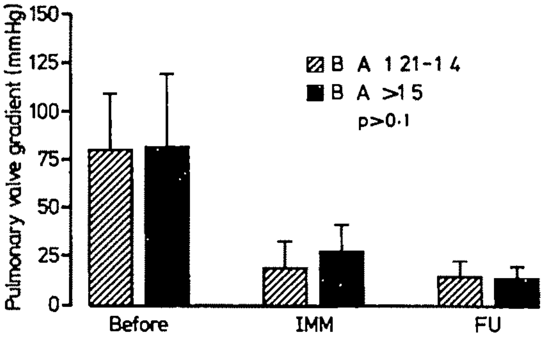

Fig 4 *The peak systolic pressure gradient across the pulmonary valve before balloon dilatation and pulmonary valve gradients immediately (IMM) after dilatation and on intermediate term follow up (FU) were similar (p > 0·1) in both groups with balloon/annulus ratios of 1·21—1·4 and > 1·5.*

Discussion

It is generally agreed that it is better to use balloons with diameters larger than pulmonary valve annulus for balloon dilatation of pulmonary valve stenosis.[1 2] Balloon sizes 1·2–1·4 times the pulmonary annulus are recommended[1 2] but there are no hard data to support such a recommendation. Experimental evidence indicates that the balloons > 1·5 times size of the diameter of pulmonary valve annulus may damage the right ventricular outflow tract.[3] The current study was designed to confirm that it is better to use balloons that are larger than the pulmonary valve annulus to relieve stenosis of the pulmonary valve and to determine what size of balloon is needed for successful balloon dilatation of the pulmonary valve.

My results confirm that balloons larger than pulmonary valve annulus are needed to produce sustained relief of pulmonary valve obstruction. Breakdown of group 2 (larger balloon) into three subgroups showed that there is still a considerable degree of residual obstruction in the group with balloon/annulus ratio of 1·01–1·2. Intermediate term results were similar in the subgroups with balloon/annulus ratios of 1·21–1·4 and > 1·41. Balloons more than 1·5 times the size of the pulmonary valve annulus did not give better immediate or intermediate term results and may damage the right ventricular outflow tract.[3] The present data show that balloons that are less than 1·2 times the size of the pulmonary valve annulus are likely to be associated with residual pulmonary valve obstruction on follow up and cannot be recommended. Balloons that are > 1·5 times larger than pulmonary valve annulus do not have any additional advantage and therefore are not necessary. Thus balloons which are 1·2–1·5 times larger than the pulmonary valve annulus are the best for relieving pulmonary valve stenosis.

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Fetal complete heart block

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SUMMARY In a series of over 6000 patients referred for fetal echocardiography during an eight year period, 37 fetuses were found to have complete heart block. There were 16 cases of isolated heart block and 21 cases associated with structural heart disease. All mothers of fetuses with isolated complete heart block had evidence of circulating syndrome Sjögren A antibody (Ro). Only one mother had clinical evidence of connective tissue disease. In the 21 cases associated with structural heart disease there were 17 cases of atrioventricular septal defect, one case of secundum atrial and perimembranous ventricular septal defects, two cases of tetralogy of Fallot, and one case of pulmonary stenosis. All fetuses with atrioventricular septal defects and complete heart block had left atrial isomerism. Additional abnormalities of the great arteries were often found in this group; these were double outlet right ventricle, transposition of the great arteries, pulmonary atresia, coarctation of aorta, and stenosis of the pulmonary or aortic valves. Intrauterine congestive heart failure was a feature of four cases in the group with isolated complete heart block and 11 cases of the group with associated structural heart disease. The outcome in the fetuses with isolated complete heart block was better than in those with heart disease: 12 of the 16 fetuses are alive, two of them have a pacemaker. But only three of the group of 21 fetuses with cardiac malformation are alive, and two of them have a pacemaker.

Complete heart block was first described as "impaired atrioventricular syndrome" by Morquio in 1901.[1] The condition was characterised by a slow pulse, syncopal attacks, and sudden death. Since then many workers have reported cases of isolated complete heart block and its association with structural heart lesions.[2-4] Hull *et al* in 1966 recognised the relation between maternal systemic lupus erythematosus and complete heart block; they described a child born to a mother with active lupus.[5] More recently a strong association has been found between isolated infantile complete heart block and the presence of syndrome Sjögren A antibody in maternal serum.[6 7] This antibody is also known as Ro, after the patient in whom it was first detected.[8]

The first case of fetal heart block was reported by Plant and Steven in 1945.[9] The diagnosis was suspected by fetal heart auscultation and fetal electrocardiogram. Fetal heart block can now be detected by M mode and Doppler echocardiographic examination.[10 11] Structural heart defects in the fetus can be seen by cross sectional echocardiography.[12 13] The association between atrioventricular septal defect, left atrial isomerism, and complete heart block has been described previously in both postnatal and prenatal life.[14 15] We describe a series of cases of complete heart block diagnosed in prenatal life, with the associations and outcome of these cases.

Patients and methods

During an eight year period over 6000 fetal echocardiograms were performed in our department. All cases were referred because the fetus was considered to be at increased risk of structural heart disease. The reasons for referral included a family history of congenital heart disease, maternal diabetes, exposure to cardiac teratogens, the detection of fetal arrhythmia, non-immune hydrops, or an abnormal heart structure suspected on a routine scan. We found complete heart block in 37 fetuses.

Fetal echocardiography was performed with an Advanced Technical Laboratories Mark 4 sector scanner or a Hewlett-Packard 77020A phased array system with a 5 mHz transducer. The fetal heart was visualised and cardiac structure was established. The

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rhythm and heart rate were identified by directing the M line through the aorta and left atrial wall. Atrial systole was demonstrated by movement of the atrial wall towards the aortic root. Ventricular systole was identified by the opening of the aortic valve. The relation between atrial and ventricular contraction was established and complete heart block diagnosed in those fetuses in which there was complete dissociation between atrial and ventricular contraction. In fetuses with isolated complete heart block we examined maternal serum for syndrome Sjögren A antibody.

Results

Sixteen of the 37 cases of fetal heart block that we detected had no other abnormality and 21 had associated structural cardiac disease. The gestational age at diagnosis ranged from 17 to 38 weeks. There were 35 singleton pregnancies and one case of twins. Each twin had isolated heart block.

All mothers with fetuses who had isolated complete heart block had positive titres of skin sensitising antibodies. One mother had clinical evidence of Sjogren's syndrome. There was no correlation between maternal antibody titre and outcome in these cases. In the 16 with isolated complete heart block the reason for referral in all cases was because the obstetrician had detected an irregular fetal cardiac rhythm or bradycardia on a routine scan. Four of these fetuses were hydropic. In one case the pregnancy was terminated at 17 weeks because the severity of hydrops suggested a poor prognosis. In the twin pregnancy both fetuses had gross hydrops and poor ventricular function seen initially at 34 weeks' gestation. Both twins died in utero at 36 weeks' gestation. The fourth case of hydrops presented at 21 weeks' gestation. Cardiac function was poor and intrauterine death was expected. Examination of this pregnancy, however, at 26 and 30 weeks showed resolution of the hydrops and improved cardiac function.

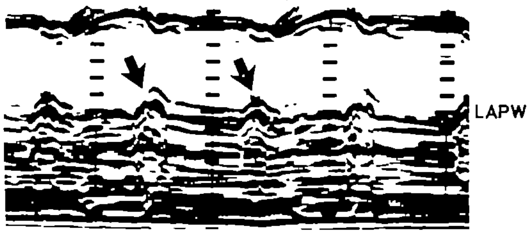

Figure *The M mode echocardiogram positioned to record the aortic valve (Ao) and left atrial posterior wall (LAPW). The larger arrows show opening of the aortic valve. Atrial contraction, indicated by the smaller arrows, is unrelated to ventricular contraction.*

Another fetus died in utero at 27 weeks' gestation four weeks after premature rupture of membranes. In the remaining 11 fetuses, the course of pregnancy was uneventful. Nine patients are alive and well and have not required a pacemaker. Two children had permanent pacemaker implantation. In one infant a cardiac arrest before pacemaker implantation caused brain damage.

The 21 fetuses with complete heart block and associated cardiac abnormality were referred for fetal echocardiography because of bradycardia in six fetuses, suspected congenital heart disease in four, the association of non-immune fetal hydrops and heart abnormality in eight, and the detection of fetal bradycardia, hydrops, and congenital heart disease in three. A complete atrioventricular septal defect was found in 17 fetuses. None was associated with chromosomal abnormality. One further fetus had a large secundum atrial and perimembranous ventricular septal defect. All 18 had left atrial isomerism. Thirteen of these 18 fetuses also had abnormalities of the great arteries. Double outlet right ventricle was found in four fetuses, transposition in one, and pulmonary atresia in two. Pulmonary or aortic stenosis was found in five and three fetuses respectively. Coarctation of the aorta was found in one. In the remaining three fetuses with structural heart disease and normal atrial situs, the diagnoses were tetralogy of Fallot in two and pulmonary stenosis in one.

Non-immune fetal hydrops was found in 11 fetuses of this group. Pregnancy was terminated in nine cases: in six there was severe hydrops in the second trimester of pregnancy with complex cardiac anomalies. Four fetuses died in utero; all were hydropic with an atrioventricular septal defect. There were two neonatal deaths within the first week of life. One neonate with an atrioventricular septal defect, left atrial isomerism, and transposition of the great arteries died on the fourth day of life and the other with an atrioventricular septal defect and left atrial isomerism died immediately after birth. There were three infant deaths, one after total correction of an atrioventricular septal defect at nine months and one other after total correction of tetralogy of Fallot at six months. The third case with an atrioventricular septal defect and double outlet right ventricle died at two years of age after a Blalock shunt operation. There are three survivors. One has an atrioventricular septal defect, left atrial isomerism, and pulmonary and aortic stenosis. Although his condition improved after pacemaker implantation, he remains in heart failure. The other case with severe tetralogy of Fallot had a pacemaker implanted at one year of age and his physical development is normal. The third survivor with pulmonary stenosis has had a successful balloon dilatation and pacemaker implantation was not required.

Discussion

Isolated fetal complete heart block has been considered to result from either an independent congenital malformation of the conduction system, maternal rheumatic disorder, or fetal myocarditis. The known association between infantile heart block and latent or symptomatic maternal connective tissue disease led us to test these mothers for syndrome Sjögren A antibody.[16-18] All cases of isolated heart block had circulating maternal syndrome Sjögren A antibody. One mother had overt Sjögren's syndrome. It has been postulated that syndrome Sjögren A antibodies, probably of the IgG class, cross the placenta and damage the fetal cardiac conduction system. Evidence of deposits of this antibody in atrial tissue suggests a direct action on cardiac tissue.[19] This may initiate an inflammatory process with a subsequent immunological response causing heart block. There is speculation about whether this immunological process interferes with normal development of the conducting tissue or damages the conducting system after it has been formed.[20 21] Our earliest case of complete heart block was detected in a fetus at 17 weeks' gestation. Histopathological features reported in seven patients born to mothers with skin sensitising antibodies[22] showed gross damage of the conduction system. In all hearts in this earlier report normal tissue in the atrioventricuar node had been replaced by fibrous and adipose tissue. Also, the sinus nodes in some of these cases were hypoplastic. The mother in our study who had Sjögren's syndrome had already had a child with this condition. In this group irregularity of fetal heart rhythm or fetal bradycardia was the main reason for referral for fetal echocardiography. However, one case was referred with suspected fetal distress because of the slow heart rate, and premature delivery had been planned. This was avoided by establishing the diagnosis of complete heart block. We recommend a fetal echocardiogram in all mothers with rheumatic disease who have syndrome Sjögren A antibody. Early detection of heart block will assist in planning appropriate obstetric management. Nine of 16 fetuses with isolated heart block are alive, symptom free, and do not require a pacemaker. Two patients are paced. It is important to recognise that complete heart block in infants is not always a benign condition. One of our patients suffered a cardiac arrest at home at the age of three months, which caused an appreciable neurological handicap. Also, pacemaker implantation in itself can be hazardous in neonates.[23]

Fetal hydrops was seen in four cases in this group. One pregnancy was terminated at 17 weeks because of the severity of hydrops and the poor prognosis. A set of twins died in utero at 36 weeks' gestation on the day an elective delivery was planned. The fourth fetus had pronounced hydrops and cardiomegaly at 21 weeks but had spontaneous regression of these findings by the subsequent examinations at 20 and 30 weeks' gestation. This observation conflicts with the common belief that the hydropic fetus with complete atrioventricular block will die in utero if left untreated. This view has prompted fetal transthoracic ventricular pacing.[24]

In a series reported in 1970, 80% of cases seen at necropsy had complete heart block in association with structural heart disease.[25] More than half of our cases seen in prenatal life had this combination. The frequency of this association in our series affected the outcome adversely. Thus of the total series of 37 cases, there are only 15 survivors of 27 continuing pregnancies. In an unselected series of children with complete heart block, only 25% had associated heart disease.[26] Our experience of spontaneous intrauterine death in a considerable proportion of patients suggests that many of these cases may pass undetected in prenatal life. The most common cardiac malformation was a complete atrioventricular septal defect. All these cases had left atrial isomerism and the polysplenia syndrome. The sinus node is a right atrial structure and pathology may show it to be hypoplastic, ectopic, or absent.[27] Also, the atrioventricular conduction system can be abnormal. In some cases, there are paired atrioventricular nodes connected by a sling of specialised conducting tissue. Malformation or absence of this sling may lead to heart block.[28-30]

The presence of conotruncal abnormalities associated with an atrioventricular septal defect was higher (82%) in our series than in other studies.[31 32] The prenatal association of atrioventricular septal defect, left atrial isomerism, and complete heart block has been described previously[15] as well as the absence of chromosomal anomalies in this disease complex. Tetralogy of Fallot seen in two fetuses was an unusual association with heart block. Fetal non-immune hydrops was a feature in more than half of the fetuses with heart disease and heart block and was the main reason for termination of pregnancy in nine patients. Four fetuses died spontaneouly in utero. There were two neonatal deaths during the first week of life and three infants died after operation. Out of eight pregnancies that continued only three patients are alive and two of them have required pacing.

In conclusion, cases of complete heart block seen in prenatal life are more likly to be associated with structural cardiac abnormalities than cases which are seen postnatally. The prognosis depends on the presence or absence of structural heart disease and the type and severity of the cardiac malformation. In general, fetuses with associated heart disease have a poorer prognosis than those with isolated complete heart block.

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Responses to carotid sinus stimulation before and after propranolol

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SUMMARY The response to carotid sinus stimulation was studied in nine elderly men (mean age 67) with no history of cardiac disease, dizziness, or syncope. The response to manual carotid sinus pressure (during one of two studies) was positive (an RR interval of > 3s) in three men. But seven men showed positive responses after intravenous propranolol (0·1 mg/kg). Similarly, the RR interval was lengthened by > 10 ms/mm Hg in two men during neck suction. Neck suction produced a positive result in four men after intravenous propranolol.

The detection of hypersensitivity of the carotid sinus in a high proportion of apparently healthy men, especially during β blockade, suggests that an abnormal response to carotid sinus massage may not be a reliable indicator for pacemaker treatment.

Since Weiss and Baker in 1933 described hypersensitivity of the carotid sinus as a cause of syncope[1] there has been considerable controversy about the importance of this sign.[2] Even though carotid sinus massage is an unphysiological stimulus that is difficult to measure it is widely used in the absence of an easily applied and more scientific method. Carotid sinus hypersensitivity—that is an RR interval of more than three seconds during carotid sinus massage—in patients with unexplained syncope is often used as an indication for pacemaker treatment.[3] The combination of unexplained syncope and carotid sinus hypersensitivity is called the carotid sinus syndrome. The results of earlier studies of the response to stimulation of the carotid sinus in healthy older people are conflicting, possibly because they used different techniques.[4-7]

Patients and methods

We studied nine elderly men (mean (SD) age of 67 (4) years (range 61–71) with no history of cardiac disease, dizziness, or syncope. An extensive non-invasive cardiac evaluation, including physical examination, twelve-lead electrocardiograms, chest *x* ray, an exercise test, echocardiography, and routine blood tests, was performed to exclude important heart disease. In addition, a Doppler investigation of the carotid bifurcation was performed to rule out the possibility of clinically important narrowing of the carotid arteries. All the men were electrocardiographically monitored for 24 hours. A tenth, otherwise apparently healthy man, who was found to have spontaneous asymptomatic complete atrioventricular block with an RR interval of between 3·1 and 4·2 s, was excluded. Informed consent was obtained from all the men and the study was approved by the local ethics committee. Table 1 shows the characteristics of the patients.

Manual pressure was applied to the carotid sinus for five seconds, three times on each side of the neck, without abolishing the ipsilateral temporal artery pulse. The procedure was performed before and after an intravenous injection of propranolol (0·1 mg/kg) on two occasions at least one month apart with the patient in both the supine position and with a head-up tilt at 60°. Recordings were made between 5 and 40 minutes after the full dose of propranolol had been given. Manual carotid pressure was applied by the same investigator and the patients were randomly chosen to start the investigation in the supine position or with head up tilting.

At the first investigation a negative pressure of − 40 mm Hg was also applied to the front of the neck, by a neck suction device;[9] this was done three times, for one minute each time. The instrument that we

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Table 1 *Characteristics of elderly men who were tested by carotid sinus massage*

Subject	*Age (y)*	*Weight (kg)*	*Height (cm)*	*Exercise test* (W)*	*LVEDd (mm)*	*RHV (ml/m²)*	*LTER (s)*
1	61	78	182	180	44	330	1·2
2	60	86	183	218	48	460	1·4
3	70	65	178	190	42	450	1·1
4	71	77	174	170	42	430	1·3
5	67	75	182	192	49	520	1·1
6	68	88	182	224	48	410	1·3
7	68	73	169	180	48	430	1·4
8	65	65	172	260	46	440	1·5
9	65	75	172	210	48	480	1·1

*Bicycle test with a continuous increase in work load of 10 W/min, LVEDd, left ventricular end diastolic diameter measured by echocardiography; RHV, relative heart volume measured by chest *x* ray and expressed as ml/m² body surface area;[8] LTER, longest RR interval on long term echocardiographic recording.

used is a modified version of Eckberg's neck suction device moulded in lead that can be adjusted to fit different people without producing positive pressure near the carotid vessels.[10] A negative pressure of −40 mm Hg was achieved within 300 ms. The electrocardiogram was monitored throughout the study and at the first investigation the brachial arterial pressure was recorded on a Siemens Elema Mingograf 81. The maximum RR intervals seen during manual carotid pressure are reported. A corrected carotid sinus inhibitory time—maximum RR interval minus basic cycle length—was calculated to correct for the underlying heart rate and to allow comparison with the findings during neck suction, and also between head up tilting and the supine position, and between the two occasions. Lengthening of the RR interval during neck suction is given as ms/mm Hg negative pressure and was calculated as the longest RR interval minus the basic RR interval divided by 40 mm Hg.[11]

STATISTICAL ANALYSIS

The results are expressed as mean (SD). Differences between various procedures were tested by the paired Student's *t* test. A p value <0·05 was regarded as significant.

Results

Table 2 shows the responses to manual carotid

Table 2 *Responses to manual carotid pressure and neck suction before administration of propranolol*

Subject	*max RR1 (s)*	*max RR2 (s)*	*CCSI1 (s)*	*CCSI2 (s)*	*RRip (ms/mm Hg)*
			Supine position		
1	1·25	2·20	0·41	1·34	4·75
2	1·53	4·90	0·61	4·08	4·25
3	1·56	1·42	0·59	0·54	3·50
4	1·82	1·80	0·67	0·64	6·25
5	1·48	2·62	0·38	1·72	8·00
6	2·70	1·78	1·60	0·76	6·00
7	6·96	4·78	5·60	3·86	12·00
8	3·82	5·50	2·64	4·26	18·00
9	1·34	1·14	0·34	0·24	3·00
mean (SD)	2·50 (1·87)	2·90 (1·70)	1·43 (1·74)	2·11 (1·68)	7·31 (4·86)
			Head up tilt		
1	1·01	1·04	0·24	0·34	3·50
2	0·80	5·62*	0·12	4·88	4·50
3	1·53	3·84	0·62	3·14	1·25
4	1·54	1·30	0·75	0·94	2·00
5	1·36	1·68	0·50	0·44	7·00
6	1·92	1·80	1·10	0·74	8·00
7	6·96*	3·08	6·18	2·46	4·00
8	3·20	3·10	2·32	2·32	10·00
9	1·12	0·78	0·22	0·10	5·50
mean (SD)	2·16 (1·93)	2·47 (1·58)	1·34 (1·94)	1·53 (1·62)	5·08 (2·85)

max RR, maximum RR interval; CCSI, corrected carotid sinus inhibition time; RRip, RR interval prolongation during neck suction; 1, first investigation; 2, second investigation.

*Vertigo.

Table 3 *Responses to manual carotid pressure and neck suction after administration of propranolol*

Subject	*max RR1 (s)*	*max RR2 (s)*	*CCSI1 (s)*	*CCSI2 (s)*	*RRip (ms/mm Hg)*
			Supine position		
1	1·19	4·68	0·24	3·66	3·25
2	6·10	7·30	5·15	6·28	8·50
3	1·89	7·04	0·76	5·92	5·50
4	4·55	3·06	3·33	1·78	6·75
5	6·00	6·28	4·45	5·22	17·50
6	2·24	2·18	0·94	0·78	10·25
7	7·42	10·20†	6·08	9·08	15·50
8	5·20	7·52	3·80	6·12	31·00
9	1·42	0·94	0·22	0·14	3·00
mean (SD)	4·00 (2·34)	5·47 (2·98)	2·77(2·27)	4·13 (3·10)	11·25 (8·95)
			Head up tilt		
1	1·08	1·84	0·18	0·98	2·25
2	6·10	6·54*	5·15	5·54	4·50
3	2·60	2·00	1·63	1·10	3·00
4	4·20	1·92	3·24	0·78	3·75
5	6·66	5·50	5·51	4·56	10·25
6	2·86	1·80	1·86	0·52	12·50
7	7·18†	5·94	5·98	5·04	4·50
8	1·76	4·62	0·48	3·48	11·00
9	1·18	1·00	0·14	0·04	3·50
mean (SD)	3·74 (2·39)	3·46 (2·15)	2·69 (2·36)	2·62 (2·27)	6·14 (3·94)

See footnote to table 2 for abbreviations.

*Vertigo. †Syncope.

pressure and to the negative pressure applied with the neck suction device before administration of propranolol and table 3 shows the responses after propranolol. No fall in blood pressure independent of heart rate was noted. Syncope or dizziness occurred in two men (2 and 7). None of the men developed any cardiac symptoms during a median follow up of 15 months (range 7–20) from the first investigation.

As the first investigation, during manual carotid pressure two subjects had RR intervals of >3 s (3·8–7·0 s) before propranolol and five (4·6–7·4 s) after propranolol administration. At the second investigation three subjects had RR intervals of >3 s (4·8–5·5 s) before and seven (3·1–10·2 s) after propranolol administration (fig 1). The difference between the maximum RR intervals before and after administration of propranolol was statistically significant both in the supine position and with 60° head up tilt ($p < 0{\cdot}05$) at the first investigation, but only in the supine position ($p = 0{\cdot}003$) during the second study. In the supine position there was a statistically significant difference between the corrected carotid sinus inhibition time before and after propranolol administration at both the first and second investigation ($p = 0{\cdot}034$ and $p = 0{\cdot}003$ respectively). Maximum lengthening of the RR interval during neck suction was $>$ 10 ms/mm Hg negative pressure in two subjects (12–18 ms/mmHg) before and in four subjects (10–31 ms/mm Hg) after propranolol administration. The difference in the lengthening of the RR interval both before and after administration of propranolol was statistically significant ($p = 0{\cdot}017$) in the supine position (fig 2).

Responses to manual pressure, expressed as corrected carotid sinus inhibition time, were significantly different in the head up tilt and the supine positions, only after propranolol administration during the second investigation ($p = 0{\cdot}006$). During neck suction the prolongation of the RR interval was significantly longer in the supine position than in the head up tilt position after propranolol administration ($p = 0{\cdot}027$). There was a good correlation between the corrected carotid sinus inhibition time during manual carotid pressure measured in the supine position and in the head up tilt on the two occasions both before and after propranolol administration (the four r values ranged from 0·66 to 0·99; $p < 0{\cdot}05$) (fig 3). A similar correlation was found during neck suction (r values 0·61 and 0·69; $p < 0{\cdot}05$).

Lengthening of the RR interval during neck suction only correlated with corrected carotid sinus inhibition time when measured in the supine position ($r = 0{\cdot}67$, $p = 0{\cdot}023$) before propranolol administration. Comparison of the corrected carotid sinus inhibition times measured on two occasions showed a

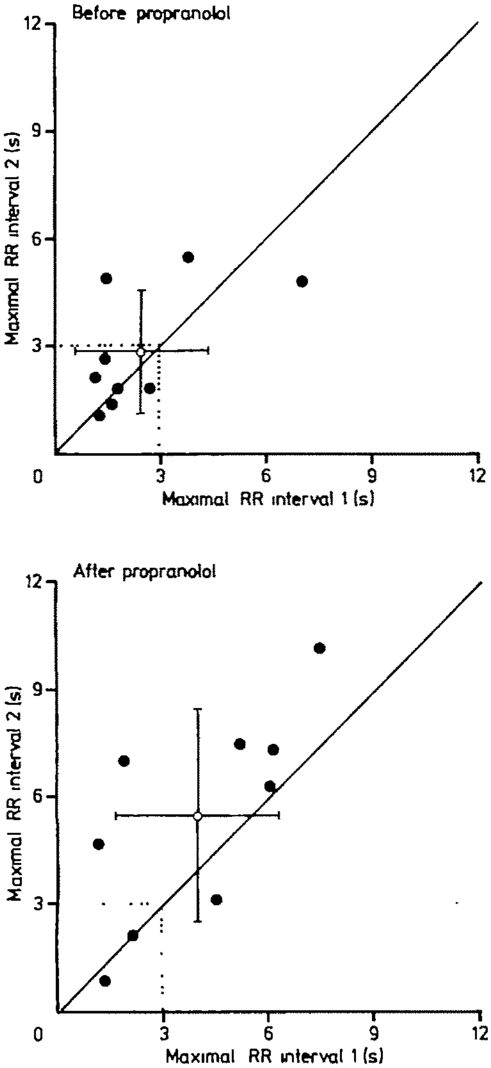

Fig 1 *Maximum RR intervals during manual carotid pressure in the supine position before and after propranolol administration. Individual values, means, and standard deviations are given. The differences between results before and after propranolol administration are significant First investigation (1) p = 0·025 and second investigation (2) p = 0·003.*

correlation only after propranolol administration (supine position: r = 0·71, p = 0·016; head up tilt: r = 0·77; p = 0·008).

Discussion

The association between hypersensitivity to the

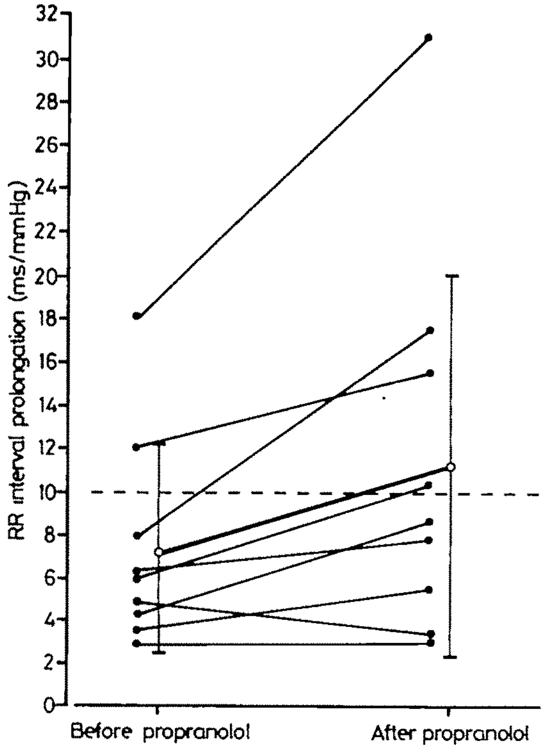

Fig 2 *Prolongation of the RR interval during neck suction Individual values, means, and standard deviations are given (p = 0·017)*

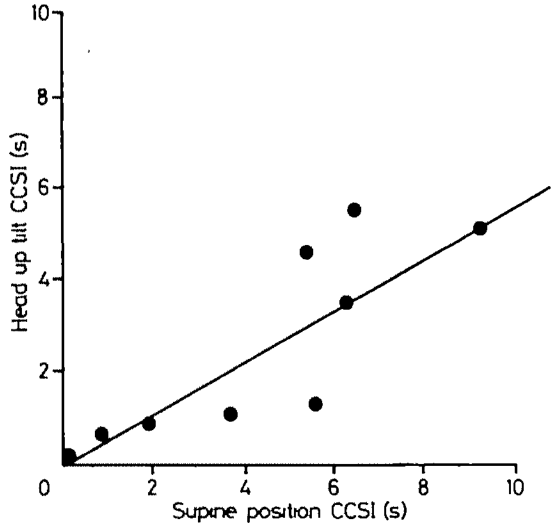

Fig 3 *Correlation between corrected carotid sinus inhibition time (CCSI) in the supine position and during head up tilt at the second investigation after propranolol administration (r = 0·82; p = 0·004)*

carotid sinus reflex and spontaneous syncope has long been recognised.[1] The introduction of pacemaker treatment, with excellent results in patients with the cardio-inhibitory form of the carotid sinus syndrome, has evoked new interest in this condition.[12 13] Carotid sinus hypersensitivity in combination with unexplained syncope is a widely accepted indication for pacemaker treatment. The number of patients diagnosed as having carotid sinus syndrome, however, varies considerably and this syndrome accounts for between 0·5% and 12% of all pacemaker implantations in different reports.[14] These differences probably reflect several difficulties in the evaluation of the cardiac response to carotid sinus massage. Firstly the reproducibility of carotid massage is low,[15 16] and secondly the symptoms vary spontaneously.[17] Furthermore, a spontaneous recovery in 50% of patients with a diagnosis of carotid sinus syndrome has been reported.[18] In other studies spontaneous remission rates in syncope ranging from 67 to 100% have been found.[19-21] All of a subgroup of patients with unexplained syncope recovered.

There have been few studies of the normal response to carotid massage and the results are conflicting.[1 4-8 12] It is difficult to establish an unequivocal diagnosis with an unphysiological test that is difficult to quantify. A more scientific test that uses an airtight neck collar to apply a negative pressure has therefore been suggested. When the RR interval is prolonged by more than 10 ms/mm Hg negative pressure the response is regarded as abnormal.[11]

We used both manual pressure on the carotid sinus and a neck suction device in our study. Carotid pressure was applied according to recent recommendations.[3] To minimise variations in the technique the same person always applied the carotid pressure. Hypersensitivity of the carotid sinus was noted in three apparently healthy subjects, a finding that casts doubt on the claim that the current manual carotid test discriminates between normal and abnormal responses.[3 7] We would have to follow up these three patients for several years to find out whether their results should be regarded as normal or as indicating a pre-symptomatic phase. If the explanation for the discrepancy between our results and those of other investigations lies in differences in technique, this is further evidence for difficulties in standardising carotid massage. In addition, the comparison between the results obtained on two different occasions confirms previous reports that the reproducibility of the carotid test is low. Application of the suggested criterion for an abnormal response during neck suction to our patients reduced the number of abnormal responders to two.[11] Our results do not detract from the evidence of an association between syncope and carotid sinus hypersensitivity, but because we found positive tests in a significant number of apparently healthy individuals, abnormal test results should not automatically lead to active treatment.

There was a good correlation between the corrected carotid sinus inhibition time in the supine position and with head up tilting during all six test periods in our study. This indicates that stimulation of the carotid sinus was consistent. After administration of propranolol the results were considerably different. RR intervals of more than 3 s were noted in seven men and four showed an abnormal response to neck suction. One of these four men responded normally to the manual carotid test. But others found that intravenous administration of a β blocker did not enhance the response to carotid massage in patients with carotid sinus hypersensitivity.[22]

If we assume consistent stimulation of the carotid sinus throughout our study, our results suggest that alteration of the sympathetic response may be responsible for lengthening of the RR interval. This suggestion accords with the lack of difference between the degree of RR prolongation before and after β blockade in patients with carotid sinus hypersensitivity.[22]

Little is known about the influence of β blockade on autonomic sympathetic activity, and different groups of neurons respond differently. Administration of metoprolol increased sympathetic activity in muscle.[23] Earlier studies showed considerable but transient sympathetic responses in the muscles to changing levels in afferent baroreceptor impulses.[24 25] During alternating high and low neck suction an increase in suction inhibited sympathetic outflow, and a fast onset of neck suction led to short term total inhibition of sympathetic activity. These interesting findings suggest a highly speculative explanation for the considerable lengthening of the RR interval after administration of propranolol—a result that simulated hypersensitivity of the carotid sinus. Blockade of the β receptors might increase sympathetic outflow, possibly with a concomitant increase of parasympathetic activity. In this situation a sudden withdrawal of the sympathetic nerve activity to the heart might lengthen the RR interval.

In conclusion, three of nine apparently healthy elderly men showed carotid sinus hypersensitivity—that is RR intervals of more than three seconds during carotid sinus massage or lengthening of the RR interval by more than 10 ms/mm Hg during neck suction. After β blockade seven of the nine men showed carotid sinus hypersensitivity. This suggests that an alteration in sympathetic nerve activity may be responsible for the physiological mechanisms that cause prolonged RR intervals. Whatever the true explanation for these results, they indicate that a positive test for carotid sinus sensitivity should not automatically prompt active treatment.

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Anomalous left coronary artery arising from the pulmonary artery in infancy: Is early operation better?

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SUMMARY From January 1975 to January 1987, 21 consecutive infants aged less than six months (mean (SD) 2·6 (1·2)) were admitted with anomalous origin of the left coronary artery from the pulmonary artery. In the first 12 patients, who were seen up to 1982, operation was performed after the age of one year (mean (SD) 29 (29) months) (group 1). The next nine infants, seen from 1983 to 1987, had their operations within a few weeks of the onset of symptoms (mean (SD) age 4·8 (1·4) months) (group 2). In group 2 the left coronary artery was relocated into the aorta, whereas in group 1 there was additional resection of the left ventricular wall or mitral valvoplasty or both. At presentation there were no differences in age, clinical condition, heart enlargement, and echocardiographic left ventricular dysfunction between groups 1 and 2. Seven of the 12 patients in group 1 died, five while they were awaiting operation (three died suddenly at home) and two at operation. The five survivors are doing well 6·4 (3·1) years after operation with normal left ventricular function which improved slowly over several months after operation. Two of the nine patients in group 2 died; both deaths occurred at or soon after operation. The seven survivors are doing well 1·8 (0·9) years after operation. In three, left ventricular function recovered within three weeks; and there was even partial or total regression of the Q waves in the supposedly necrotic areas. In the remaining four the pattern of improvement in left ventricular function resembled that in group 1.

Operation should be undertaken early in infants with anomalous left coronary artery arising from the pulmonary artery because the procedure is relatively safe, prevents a high natural mortality, and offers a better chance of a faster recovery of left ventricular function.

Anomalous origin of the left coronary artery from the pulmonary artery is a rare severe congenital anomaly that often causes myocardial infarction within a few weeks of birth with subsequent ventricular dysfunction, mitral valve incompetence, and severe congestive heart failure.

There is disagreement about when to operate and whether prompt restoration of a systemic left coronary artery perfusion is important. There have been numerous conflicting reports about the risks of medical treatment and early operation. With medical treatment, mortality in the first year of life ranges from 35%[1] to 80%[2] or even 90%.[3] But many are afraid to risk open heart surgery in severely ill infants[1 4] when they know that the operation may not be successful because myocardial infarction has usually already occurred. Nevertheless, others favour a vigorous approach with early operation,[2 5–7] arguing that restoration of a two coronary artery system will protect against sudden death, may lead to the quick recovery of good ventricular function,[8] and avoid the late development of atherosclerosis.

These discrepancies may be attributable to the large differences in the clinical condition of the various patient populations. In some centres, only

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very ill patients are selected for operation[1] and so the outcome with medical treatment is better; in others only the healthiest patients have operations[4] and the outcome is better than with medical treatment.

We used to treat very ill infants with large myocardial infarction caused by anomalous left coronary artery arising from the pulmonary artery by a medical protocol with delayed operation (after one year of age) but since 1982 we have been operating earlier. We have examined the results of these two treatments.

Patients and methods

From January 1975 to January 1987, 21 consecutive infants (three weeks to six months old, mean (SD) 2·6 (1·2) months) were admitted to our department during or soon after a myocardial infarction caused by an anomalous left coronary artery arising from the pulmonary artery.

In all patients the diagnosis was suspected because the standard electrocardiogram showed a constant deep Q wave in leads I and aVL and sometimes in other leads too. Since 1982 cross sectional echocardiography and Doppler echocardiography have been used to identify a dilated right coronary artery, and in some the image showed continuous flow in an anomalous left coronary artery arising from the pulmonary artery. In all the patients the diagnosis was confirmed by angiography. In five the left coronary artery was seen by a direct stop-flow injection of contrast medium into the pulmonary artery[9]; in three the left ventricle could be entered through a patent foramen ovale and the abnormal vessel was imaged on a left ventriculogram; in the last 13 patients retrograde aortography was needed to assess the anomaly. The patients were separated into two groups according to how they were treated.

The first 12 infants were treated medically and operation was delayed until they were at least one year old (group 1). All patients but one were admitted before 1983. This infant, admitted in 1985, had a minute left coronary artery with no arterial shunting and we decided that reimplantation would be inappropriate. The survivors were operated on at a mean age of 29 (29) months (range 14–108 months).

The next nine infants had operations 0·5–4 months after the myocardial infarction. The mean (SD) age at operation was 4·8 (1·7) months (group 2). All patients but one were admitted after January 1983. This child, admitted in 1977, had intractable heart failure with massive mitral insufficiency and a left ventricular aneurysm.

Table 1 summarises the clinical data on the patients in both groups when they were first seen in our department. All had evidence of myocardial infarction at admission and were in congestive heart failure, which in 13 was severe enough to cause low systemic output. There were no significant differences in age, clinical state, heart enlargement, or electrocardiographic findings between the two groups at that time.

Table 2 summarises the surgical management. Survivors in group 1 had an extensive operation for relocation of the left coronary artery into the aorta and also eventually resection of the left ventricle or mitral valvoplasty or both.[4] All infants in group 2, except the patient operated on in 1977, had only relocation of the left coronary artery into the aorta.

The surgical technique has been described elsewhere.[7] The left coronary artery was transferred together with a sizable cuff of the pulmonary artery wall from around the ostium and was directly reimplanted, without tension, into the aorta. End to end reconstruction of the pulmonary artery was then achieved by mobilisation of the pulmonary bifurcation. In all cases the operation was performed on bypass and hypothermia. After 1983 (the last six patients) operation included 2–6 hours of left ventricular assistance on bypass at the end of the operation.

All but two of the survivors were followed up at our outpatient clinic. Two were followed up elsewhere. Every three months during the first year and then

Table 1 *Preoperative data in 21 infants with anomalous left coronary artery arising from the pulmonary artery (mean (SD))*

			Clinical		*Chest x ray*	*Echocardiography*		
*Group**	*No of cases*	*Mean age (months)*	*LCO*	*AVS*	*(mean CTR)*	*No of cases*	*LVDD (mm)*	*ShFr (%)*
1	12	2·7 (1·4)	7	8	0·69 (0·03)	6	42 (4)	12 (3)
2	9	2·5 (1·3)	6	6	0·70 (0·03)	9	44 (4)	13 (4)
p value		>0·5	>0·5	>0·5	>0·5		>0·5	>0·5

*See text for definitions of groups 1 and 2.
AVS, artificial ventilation support; CTR, cardiothoracic ratio; LCO, low cardiac output, LVDD, left ventricular end diastolic diameter (M mode); ShFr, shortening fraction of the left ventricular diameter
p Values apply to comparisons between group 1 and group 2.

Table 2 *Surgical procedure in 16 infants with anomalous left coronary artery arising from the pulmonary artery*

		On the coronary artery			*Associated operation*		
*Group**	*No of cases*	*LCAR*	*Lig*	*SCAAn*	*LV res*	*MV pl*	*Both*
1	7	5	0	2	5	1	1
2	9	9	0	0	1	0	0

*See text for definition of groups 1 and 2
LCAR, relocation of the left coronary artery into the aorta; Lig, ligation of the left coronary artery, LV res, left ventricular resection; MV pl, mitral valvoplasty, SCAAn, anastomosis of subclavian artery to left coronary artery.

once a year each operated child was examined and had a chest *x* ray, standard 12 lead electrocardiogram, M mode and cross sectional echocardiography (since 1980), and pulsed Doppler study (since 1986). In addition, two of the survivors had retrograde aortography to assess the patency of the left coronary artery.

The results was evaluated by the analysis of variance between the two groups for the condition at admission to hospital and by χ^2 for mortality in the two groups.

Results

GROUP I

Five (42%) of the twelve infants died between four and nine months of age. Two had not recovered from the first episode despite intensive medical treatment including artificial ventilation; they had massive myocardial infarction with mitral insufficiency. The other three died at home after discharge from our unit on medical treatment (digoxin and frusemide) for controlled heart failure. They had persistent cardiomegaly and a dilated hypokinetic left ventricle. They were awaiting operation at the age of about two, which was thought to be the optimal age for operation. One died from infective pneumonia and the other two died suddenly from a presumed ventricular arrhythmia.

The remaining seven patients survived beyond the first year of life. They were discharged from the hospital after 3–7 weeks with controlled (six) or moderate (one) congestive heart failure with massive cardiomegaly (mean (SD) cardiothoracic ratio 0·66 (0·03)) and an hypokinetic left ventricle. They all had an operation between the age of 14 to 102 months (mean (SD) 29 (29) months), and at that time cardiomegaly was still present (fig 1). Two died at or soon after operation, which was extensive with left ventricular resection and, in one, mitral valvoplasty. Five survived the operation and have been followed for 4–11 years (6·4 (3·1) years). All are doing well with no symptoms and mild cardiomegaly which decreased progressively over one year (fig 1); three have recovered normal left ventricular function; M mode echocardiography showed a left ventricular shortening fraction of 30%, 32%, and 35%.

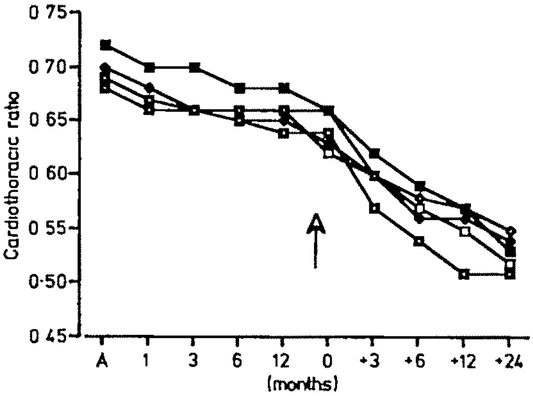

Fig 1 *Heart size (cardiothoracic ratio) in the five survivors of late operation (group 1). A, admission to hospital; O, operation (arrow).*

Seven (58%) of the 12 patients in group 1 died. Aortography in two of the five survivors showed a patent left coronary artery. In the remaining three the left coronary artery was seen on cross sectional echocardiography. None of the survivors has signs of aortic insufficiency or supravalvar aortic or pulmonary stenosis.

GROUP 2

Two (22%) out of the nine infants died at or shortly after operation. One was the baby admitted in 1977 who had a extensive operation for a massive infarction with mitral insufficiency. The second underwent isolated reimplantation of the anomalous left coronary artery and died three weeks after operation from a severe pulmonary infection. At that time he had partly recovered, with a significant decrease of the cardiomegaly (cardiothoracic ratio 0·67 *v* 0·72) and a moderate increase in the left ventricular shortening fraction (16% *v* 9%).

The remaining seven patients survived operation and have been followed up for 7–45 months (mean

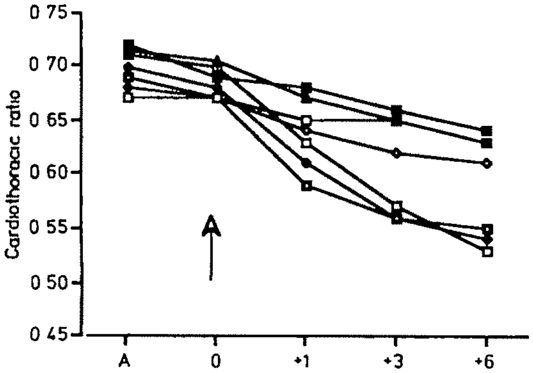

Fig 2 *Heart size (cardiothoracic ratio) in the seven survivors of earlier operation (group 2). A, admission to hospital, O, operation (arrow).*

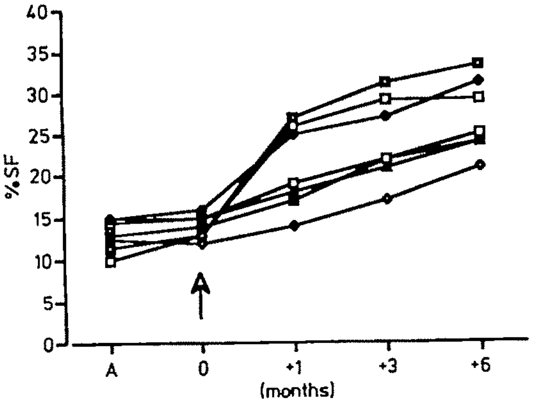

Fig 3 *Left ventricular shortening fraction in the seven survivors of earlier operation (group 2). A, admission to hospital; O, operation (arrow); %SF, shortening fraction of the left ventricular diameter on M mode echocardiography.*

(SD) 20 (11) months). They are all well. In three patients there was a considerable improvement. Within one month heart failure disappeared, cardiomegaly decreased with a reduction in mean (SD) cardiothoracic ratio from 0·68 (0·01) to 0·57 (0·02) (fig 2), and the mean (SD) left ventricular shortening fraction increased from 13 (12%) to 27 (5)% (fig 3). The electrocardiogram showed some improvement in the infarction pattern in two patients and complete recovery in one in whom R waves reappeared in leads I and aVL. In the remaining four patients the improvement was slower but constant and these children were discharged with controlled congestive heart failure. In two cardiomegaly decreased and left ventricular function was almost normal after 13 and 17 months. Follow up is short (seven and ten months) in the remaining two patients but they are improving progressively with less cardiomegaly (a fall in the cardiothoracic ratio from 0·69 to 0·63) and an improved shortening fraction (from 14% to 23%).

The overall mortality for group 2 was two (22%) out of nine. The left coronary artery was seen on cross sectional echocardiography in all five patients followed up in our department. They did not have valvar aortic stenosis or supravalvar pulmonary stenosis or any valvar insufficiency.

Discussion

At admission cardiovascular disease was equally severe in both treatment groups. We know that a statistical comparison between two consecutive groups can be criticised because the earlier patients (group 1) will not have benefited from recent medical improvements and will have had longer for late complications to appear. Nevertheless, the main improvement in medical treatment is the use of vasodilators to treat cardiac failure. This is unlikely to have improved the outcome of medically treated patients, especially as three of the five deaths occurred in patients with controlled heart failure. It is also unlikely that the shorter follow up of group 2 significantly affected the overall outcome because most severe complications, mainly sudden death, occur in the first year after infarction and not when the two coronary arteries are patent. In all but two patients in group 2 follow up exceeded one year; all had a patent left coronary artery on cross sectional echocardiography and Doppler study, and left ventricular function continued to improve in all survivors in group 2.

The difference in outcome between the two groups is so striking that early operation must have advantages. Not only was the overall mortality considerably less in group 2 than in group 1, but surgical mortality in group 2 was less than natural mortality in group 1. Also, surgical mortality was not higher in infants than in older children; this result must have been influenced by improvements in cardiac surgery in the past decade, however. The striking difference between our series and earlier one[1 3-5] is the low mortality that we found in the younger infants. This must be the result of improvements in neonatal cardiac surgery. Advances in neonatal bypass techniques, myocardial preservation, and handling of tiny coronary arteries (for anatomical correction of simple transposition of the great arteries) may have had cumulative, beneficial effects. We also believe that the systematic use of left ventricular assistance at the end of the operation was helpful, that it is important to limit the procedure to the coronary relocation in these young patients, and to avoid any other operation on the left ventricle or the mitral valve.

This study showed that even in medically treated patients who did well, left ventricular function improved only when perfusion by a double coronary artery system was restored—despite the claim that the supposed territory of the anomalous left coronary artery was said to be fibrotic. Early operation was associated in three of the seven survivors with a striking (and somewhat unexpected) improvement in the areas that were supposed to be definitively damaged by the infarction. The younger the patient the quicker the recovery of the left ventricular dysfunction. This probably reflects the enormous potential for tissue growth in infants. Now that early operation has become safer we think that this potential in infants is another argument for operating early. But how early? Should we continue to wait a few weeks or should we operate as soon as possible, perhaps even in the acute phase of the infarction, to enhance the possibility of a quick and complete recovery? Further comparative studies are needed to answer this question.

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Br Heart J 1988;60:527–9

Case reports

Isolated endocarditis of the pulmonary valve with fragmentation haemolysis

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From the Department of Medicine, University of Natal, Durban, Natal, South Africa

SUMMARY An unusual case of isolated endocarditis of the pulmonary valve complicated by fragmentation haemolysis resolved on antibiotic treatment.

Isolated infective endocarditis of the pulmonary valve is uncommon. It usually occurs with endocarditis of the tricuspid valve in heroin addicts or in patients with congenital heart disease.[1-3] However, in a recent report of 12 cases, only the pulmonary valve was affected in seven patients.[2] We report a further case of isolated infective endocarditis of the pulmonary valve. Fragmentation haemolysis was an unusual complication. It resolved during antibiotic treatment.

Case report

A 23 year old man presented with a two week history of dyspnoea on exertion and generalised swelling of the body. He had been treated at another hospital for a sore throat two weeks before. There was no family history of anaemia.

He was feverish, pale, and had slight ankle oedema. The pulse rate was 72 beats per minute and it was regular and bounding in character. The blood pressure was 130/60 mm Hg. The jugular venous pressure was elevated to 5 cm and there was hepatomegaly (3 cm). At the heart apex there was a soft, short, systolic murmur, and at the left sternal border there was a harsh, low pitched, early distolic murmur that increased on inspiration. There were no splinter haemorrhages, clubbing of the fingernails, splenomegaly, or petechial haemorrhages. The chest was clear and the fundi were normal. The initial assessment was aortic regurgitation with possible infective endocarditis.

Initial investigations showed: haemoglobin 71 g/l, white cell count 10·7 × 10^9/l, and platelet count 219 × 10^9/l. There was a reticulocytosis of 8 9% and the smear showed many fragmented red blood cells, spherocytes and schistocytes consistent with fragmentation haemolysis. Because of the red cell structure, the diagnosis was changed to aortic incompetence with haemolytic anaemia and the patient was investigated accordingly. The serum concentration of fibrin degradation product was < 12 μg/l, the urine stain did not show haemosiderin, and the serum bilirubin concentration was 8 μmol/l. The direct antiglobulin test, antinuclear factor, and serum complement were normal. There was a slight increase in erythrocyte osmotic fragility in 0·5% saline.

Repeated blood cultures during the first week showed no growth. The proportion of reticulocytes increased to 14% and the erythrocyte sedimentation rate to 95 mm/hour. Echocardiography performed one week after admission showed normal mitral and aortic valves, and large vegetations were detected on the pulmonary valve, the leaflets of which were thin and mobile (fig 1). Treatment was started with intravenous penicillin 5 megaunits six hourly and gentamicin 80 mg eight hourly. In the following week the patient's condition improved, the proportion of reticulocytes fell to 2 4% and the erythrocyte sedimentation rate to 55 mm/h. His haemoglobin concentration subsequently rose to 115 g/l. Repeat echocardiography showed vegetations still attached to the pulmonary valve. Three weeks later, while he was being treated with antibiotics, the patient became febrile and complained of right sided chest

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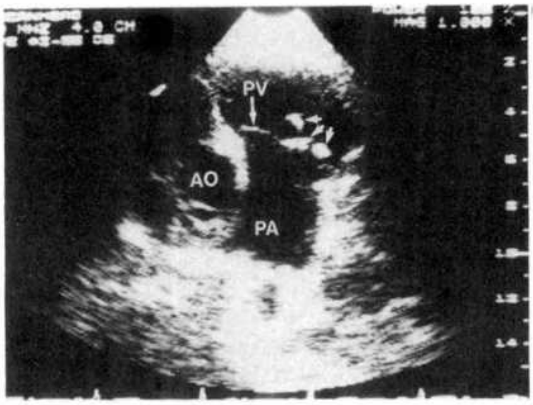

Fig 1 *Cross sectional short axis echocardiogram showing vegetations (arrows) attached to a pulmonary valve (PV) of normal appearance. AO, aorta; PA, pulmonary artery.*

pain. A chest radiograph confirmed that there was consolidation of the right lower lobe of the lung (fig 2). The erythrocyte sedimentation rate had accelerated to 95 mm/h. Antibiotics were continued and his temperature fell in the next 24 hours. Echocardiography at this stage did not show vegetations on the pulmonary valve.

The patient refused further investigation and was discharged. At follow up three months later he was symptom free but still had the murmur of pulmonary regurgitation. His haemoglobin concentration was 133 g/l and his white cell count was 5·5 × 10^9/l.

Discussion

When the pulmonary valve is affected in infective endocarditis, there is usually evidence of underlying congenital heart disease,[1-3] such as ventricular or atrial septal defect, pulmonary stenosis, and patent ductus arteriosus. More recently it has been described in heroin addicts, and necropsy studies in these patients show that the tricuspid valve is ten times more likely to be affected than the pulmonary valve.[4,5] Chronic alcoholism, skin disease, and lymphoma with depression of the immune response have been cited as other factors in the development of right sided endocarditis. None of these predisposing factors was present in this patient. A recent review noted that of 28 cases reported since 1960, only three patients had neither a predisposing event nor an underlying cardiac lesion.[1]

It is difficult to make a clinical diagnosis of infective endocarditis of the pulmonary valve: when there is pulmonary regurgitation, this is usually misdiagnosed as aortic regurgitation, or the signs may be masked by coexistent heart disease. Furthermore, the clinical picture is often dominated by pulmonary manifestations caused by emboli from the infected valve. In the later stages, as pulmonary hypertension supervenes, the murmur is indistinguishable from aortic regurgitation.[6] In our patient diagnosis was made more difficult because earlier treatment with antibiotics meant that blood cultures were negative. When endocarditis of the pulmonary valve is suspected in this situation, echocardiography is extremely useful. In the appropriate clinical setting, the demonstration of vegetations on the pulmonary valve confirms the diagnosis. Echocardiography should be performed early to avoid delay in starting antibiotic treatment. In this patient, echocardiography also helped to confirm that the findings on the chest radiograph three weeks after treatment were the result of pulmonary infarction caused by embolisation of vegetations from the pulmonary valve.

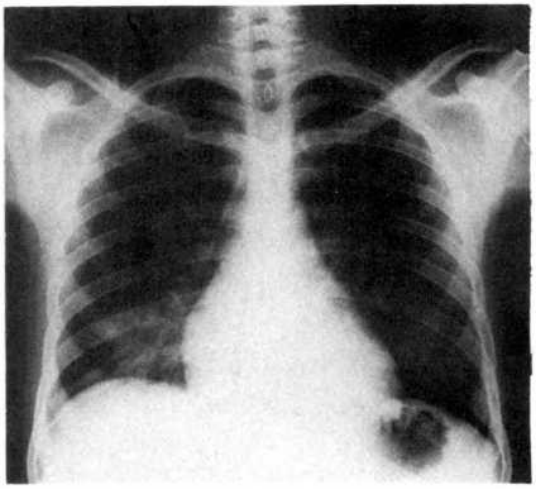

Fig 2 *Chest radiograph showing consolidation after embolisation from the pulmonary valve.*

In our patient fragmentation haemolysis was an unusual feature which initially directed attention away from infective endocarditis. Anaemia is common in infective endocarditis, and it is usually normochromic anaemia, but hypochromic microcytic anaemia is also well recognised. Fragmentation haemolysis has been described only in rare instances, and pathogenic mechanisms include disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, and mechanical damage to red cells by vegetations. Disseminated intravascular coagulation that resolved immediately after valve replacement was described in a patient with vegetations on the mitral and aortic valves.[7] In another report there was fragmentation haemolysis in two patients who had signs resembling those of thrombotic thrombocytopenic purpura that remitted with antibiotic treatment.[8] Our patient did not have signs of a bleeding tendency and his serum concentration of fibrin degradation product was < 12 µg/l. Nor did he have thrombocytopenia, renal impairment, or neurological manifestations—features indicative of thrombotic thrombocytopenic purpura. Two possible mechanisms may explain the haematological picture in this patient. Firstly, the presence of a large vegetation occluding and narrowing the valve orifice accompanied by turbulent blood flow was a contributory factor but not the only one, and secondly haemolysis seemed to be related to the infective process itself, because it began to resolve soon after antibiotic treatment was started and while the vegetation was still attached to the pulmonary valve.

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Br Heart J 1988;60:530–1

Heart block and paragonimiasis

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SUMMARY Intracardiac granulomas can cause complete heart block. A case of complete heart block is reported in a patient who had had paragonimiasis 30 years before and who had radiographic evidence of calcified granulomas in the heart and lungs.

Paragonimiasis is caused by the trematode parasite *Paragonimus westermani* which infects people who eat raw or inadequately cooked crayfish and crabs. Capsules of inflammatory and fibrous tissue form around each developing parasite. These generally cause respiratory symptoms, enteritis, and hepatitis; heart block has not been reported before.

Case report

A 63 year old white man was admitted to hospital after he lost consciousness for about five minutes. On arrival at hospital he had a further episode of cardiac syncope during which his electrocardiograph showed periods of ventricular standstill. His electrocardiogram showed complete heart block with wide QRS complexes (fig 1), and a temporary pacemaker was inserted.

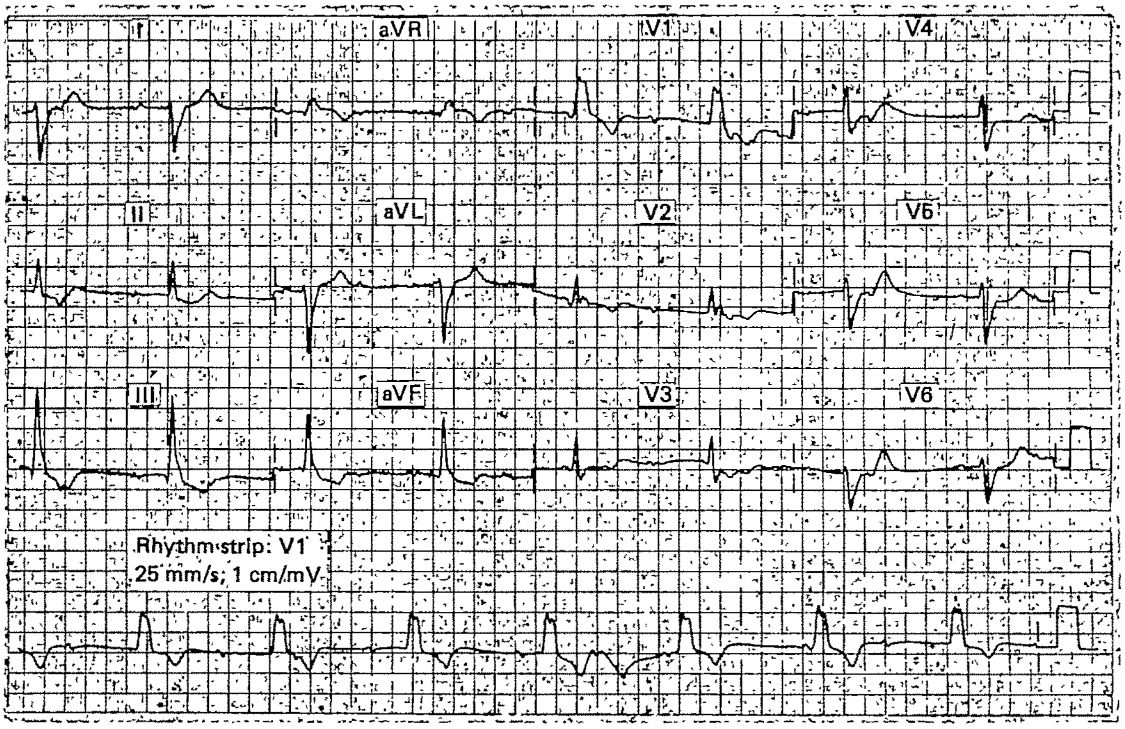

Fig 1 *Electrocardiogram on admission.*

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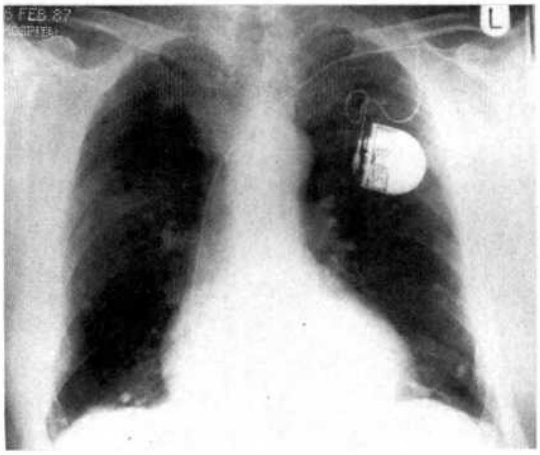

Fig 2 *Chest radiograph showing multiple calcified granulomas.*

He had had rheumatic fever at the age of 16, and while he was a prisoner of war in Korea he had had paragonimiasis from eating raw fish. He developed asthma in the 1950s, and on admission he was taking theophylline (400 mg twice a day) and prednisolone (5 mg a day), and was using salbutamol and beclomethasone inhalers.

He was a wood machinist and did not smoke. There was no family history of heart disease and he did not have a history of previous angina or syncope. He complained of severe exertional dyspnoea and of intermittent haemoptysis.

Examination showed that he was obese but he had neither cyanosis or finger clubbing. His pulse rate was 40 per minute, blood pressure was 120/70 mm Hg, and the heart sounds were soft. There was hyperinflation of the chest with generally diminished air entry, a prolonged expiratory phase, and expiratory wheezes. Abdominal and neurological examinations were normal.

Investigations showed: erythrocyte sedimentation rate 7 mm in 1 hour; haemoglobin concentration 16·4 g/l; white blood cell count 11·4 × 10^9/l (neutrophils 61%, eosinophils 2%, basophils 1%, lymphocytes 29%, monocytes 7%); serum creatinine 140 μmol/l; normal serum electrolytes and serial cardiac enzymes; Venereal Disease Research Laboratory test negative; blood glucose 5·9 mmol/l; plasma calcium 2·3 mmol/l; normal lung function tests; sputum negative for acid fast bacilli with no growth on culture; the electrocardiogram showed complete heart block with broad QRS complexes; the chest *x* ray showed multiple calcified areas, presumed to be granulomas, throughout both lung fields and cardiomegaly (fig 2); cardiac fluoroscopy showed intracardiac granulomas; echocardiography showed good left ventricular contractility with normal (non-calcified) valves and bright echoes in the region of the septum; a scintiscan of the myocardium showed that distribution of thallium was normal with no evidence of underlying myocardial ischaemia; the Kveim test was negative.

When a permanent pacemaker was inserted (Vitatron Helifix electrode, Intermedics Prima generator) it was difficult to obtain a good pacing threshold.

Discussion

This patient had evidence of calcification in the heart and lungs but no evidence of other known causes of cardiac calcification such as tuberculosis or sarcoidosis. Although we have no histological proof, we presume that the complete heart block was caused by a calcified granuloma in his conducting system—a sequela of paragonimiasis 30 years before.

Br Heart J 1988;**60**:532

Obituary

P W Duchosal

Professor Pierre Duchosal who died in Geneva on 24 April 1988 at the age of 82 was one of the world's leading cardiologists. He made important advances in clinical diagnosis, instrumentation, and organisation. His interest in techniques of investigation coupled with a practical and inventive mind led him to develop the first direct writing electrocardiograph at the age of only 23, which was followed by a multichannel recorder for phonocardiography. This heralded his mastery of cardiac auscultation and the invention with J Monti of the Didactaphone which allows simultaneous auscultation by groups of students using their own stethoscopes. This apparatus is installed in two London lecture theatres. He was also a pioneer of vector cardiography and with Sulzer he established the technique of spatial vectorial analysis. His eminence in research and teaching led to the establishment for him of the Chair of Cardiology at the Hôpital Cantonal which he occupied from 1953 to 1976. He was deeply involved with the International Society of Cardiology being secretary general for some years and ultimately president. The Swiss Foundation of Cardiology was created by his initiative to further public education and to support young research workers. He was an honorary member of the British Cardiac Society.

Professor Duchosal came from an old Geneva family and his early intention to become a violinist led to a continuing devotion to music with equal interests in archaeology and painting. He was a true humanist and a very warm hearted man whom it was always a pleasure to meet.

A Hollman
D M Krikler
P Moret

Notices

British Cardiac Society

The Annual General Meeting for 1989 will take place in Oxford on 6 and 7 April 1989, and the closing date for receipt of abstracts will be 6 January 1989.

Cardiac pacing

The 4th European Symposium on Cardiac Pacing will take place in Stockholm on 28 to 31 May 1989. Inquiries to Congrex, Box 5619, S-114 86 Stockholm, Sweden.

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